STATE OF MICHIGAN
IN THE SUPREME COURT

TERI WALTERS and KIM WALTERS,

Plaintiffs/Appellees,

-v-

S Ct No. 154489
COA No. 319016
LC No. 12-658-NH
Eaton County Circuit Court

DONALD S. FALIK d/b/a FALIK FAMILY DENTISTRY; DONALD S. FALIK, D.D.S.; ROBERT C. FALIK, D.D.S., and JANE DOE, jointly and severally,

Defendants/Appellants.
_____/

PLAINTIFFS-APPELLEES' RESPONSE TO DEFENDANTS-APPELLANTS' APPLICATION FOR LEAVE TO APPEAL (AFTER REMAND)

PROOF OF SERVICE

Respectfully submitted,

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JURISDICTIONAL STATEMENT

Plaintiffs-Appellees acknowledge this Court's jurisdiction to consider the application for leave to appeal submitted by Defendants-Appellants. However, Defendants-Appellants' mischaracterize the issue(s) before the courts below as they evaluated expert testimony on the causation of Teri Walters' onset of Wegener's granulomatosis ("WG") following several hours of intense oral exposure to highly caustic phosphoric acid accidentally supplied to Mrs. Walters in lieu of teeth whitening gel. The courts analyzed whether to admit expert evidence, and this is subject to review for abuse of discretion. However, the Court of Appeals ("COA") also analyzed the trial court's interpretation of evidentiary rules and statutes affecting admissibility of evidence, and such review is *de novo*. The COA found that the trial court had applied an improper interpretation of the rules and statutes "by effectively requiring plaintiffs to establish causation and their case prior to trial and to do so definitively." (Court of Appeals ("COA") Op. at 11.) The COA further determined that the trial court failed to take into account a host of factual issues, including the "nature, duration, intensity, and location of the exposure, the temporal proximity of the immune response to the date of exposure, and the duration and nature of an expected manifestation of WG, *i.e.*, a lengthy battle with sinusitis, which all played a role in Dr. Gershwin's overall analysis." (COA Op. on Remand (hereafter "COA Op.") at 11, **Ex. 50**.) Thus, at issue in the leave application is whether the trial court properly exercised discretion and also whether the trial court applied the correct standards before exercising its discretion.

Defendants-Appellants further misconstrue the COA's opinion by suggesting that this Court's must decide whether the Sir Bradford Hill ("SBH") methodology for determining cause supplants review pursuant to MRE 702 and MCL 600.2955. Defendants-Appellants are confusing two separate issues. The SBH methodology is a *scientific method* for evaluating cause where prospective or experimental testing is inappropriate or impossible. The SBH methodology

is not a legal test of causation and the COA did not treat it as such. Instead, the COA examined the SBH methodology within the context of MRE 702 and MCL 600.2955 (1) in order to determine whether that methodology met the reliability requirements of the court rule and statute. (COA Op. at 7-11 & nn 5-6.) The COA found that the SBH methodology was reliable and applied reliably, particularly where the scientific literature submitted establishes a statistically significant association between pesticides and WG onset, literature shows the prevalence of phosphates in pesticides, and other scientific literature links or associates exposure to fumes, particulates, pesticides, and solvents to the onset of WG. (COA Op. at 4-5, 9-11.) Therefore, the Court has jurisdiction to review the leave application, but Defendants-Appellants have misconstrued the standards at issue and applied by the COA and has misconstrued the COA use of the SBH methodology in an effort to generate new questions that do not exist.

The COA also properly distinguished *Elher v Misra*, 499 Mich 11; 878 NW 2d 790 (Dkt. No. 150824, 2016) (**Ex. 51**). The expert in *Elher* had no supporting authority to establish the reliability of his opinions and proceeded on the basis of his own belief system. The COA in the present case proceeded through eight pages of analysis of medical, scientific, and other factual support presented by Plaintiffs in support of the reliability of their expert's opinion.

COUNTERSTATEMENT OF QUESTIONS INVOLVED

I. Did the Circuit Court properly interpret and apply MRE 702 and MCL 600.2955 (1) in granting Defendants' motion *in limine* to preclude Plaintiffs' expert witness on the life-shortening autoimmune disease, Wegener's granulomatosis?

The Circuit Court answers: "Yes"

Plaintiffs/Appellants answer: "No"

Defendants/Appellees answer: "Yes"

Court of Appeals answers: "No"

II. Did the Circuit Court abuse its discretion in granting Defendants' motion *in limine* to preclude Plaintiffs' expert witness on the life-shortening autoimmune disease, Wegener's granulomatosis?

The Circuit Court answers: "No"

Plaintiffs/Appellants answer: "Yes"

Defendants/Appellees answer: "No"

Court of Appeals answers: "Yes"

III. Did the Court of Appeals correctly determine that *Elher* is distinguishable from the present case?

The Circuit Court answers: no answer

Plaintiffs/Appellants answer: "Yes"

Defendants/Appellees answer: "No"

Court of Appeals answers: "Yes"

INTRODUCTION AND SUMMARY OF ARGUMENT

Defendants again seek Court's leave to review the Court of Appeal's reversal of an order granting Defendants' motion *in limine* to preclude the testimony of Plaintiffs' expert witness, Dr. M. Eric Gershwin. The Court of Appeals ("COA") determined that the trial court erroneously found Dr. Gershwin's testimony unreliable based upon its interpretation of Michigan Rule of Evidence (MRE) 702 and MCL 600.2955 (1) and its failure to consider information provided in support of the reliability of Dr. Gershwin's testimony. Dr. Gershwin is a preeminent expert in immunology, rheumatology, and autoimmune disease, which pertain to the autoimmune disease at issue, Wegener's granulomatosis ("WG"). The COA reversed the Circuit Court ("Circuit") order precluding Dr. Gershwin's testimony that Walters suffered the onset of WG as a result of her exposure to phosphoric acid etching solution.

WG is an extremely rare autoimmune disease that may be fatal and is anticipated to reduce Walters' lifespan by ten years. WG is a form of vasculitis that causes inflammation of the blood vessels, reduces blood flow to organs, and damages the kidneys, lungs, upper respiratory tract, and blood vessels, among other things. Walters suffered the onset of WG shortly after her exposure to a caustic etching solution made of phosphoric acid. Defendants erroneously provided this phosphoric acid etching solution to Walters instead of teeth whitening solution. The etching solution is used by dentists to destroy the enamel on teeth before bonding. It is normally used only by the dentist and is never sent home with a patient. Unfortunately, Walters used the etching solution in her dental tray overnight in an attempt to whiten her teeth. This led to severe injuries, including the onset of WG.

The parties provided dozens of scientific articles to the Circuit upon which Dr. Gershwin based his opinions. Dr. Gershwin relied upon the pathology of the disease, the time frame of its onset after exposure, and studies linking similar substances to WG onset. He traced the WG

onset from effect to cause using a retrospective methodology found throughout the scientific literature as the common practice because WG is not subject to experimental testing. Dr. Gershwin's analysis also satisfies the scientifically accepted SBH methodology, which examines nine factors to determine causation when experimental testing is not possible.

Instead of evaluating scientific literature and methodologies to detect a sound basis for Dr. Gershwin's opinions, the Circuit weighed perceived inconsistencies in the scientific literature against Dr. Gershwin's opinions. By requiring uncontested scientific opinions, the Circuit established an overly rigorous standard that is not contemplated under MRE 702, MCL 600.2955 (1), or the relevant interpretive case law. The COA rejected the Circuit's misapplication of MRE 702 and MCL 600.2955 (1) upon *de novo* review and found extensive support for Dr. Gershwin's reliability in the scientific literature and factual circumstances while acknowledging that he need not negate all possible causes or achieve absolute certainty. (COA Op. at 10-11 & n 7, **Ex. 50**.)

The Circuit abused its discretion by ignoring scientific literature supporting the following key components of Dr. Gershwin's opinions and methods. (i) Genetic predisposition is necessary for the onset of WG. (ii) WG onset begins with inflammation of the upper airways, consistent with Walters' exposure to phosphoric acid. (iii) The pathological process, symptoms, and time frame of WG onset is consistent with onset in Walters after exposure to phosphoric acid. (iv) The capacity of phosphoric acid to initiate WG is supported by literature linking similar chemicals to WG onset. (v) Phosphoric substances play a central role in the immunological process that results in WG. (vi) Intense exposure to an inflammatory agent is linked to WG onset. (vii) Human and animal testing for WG causes is not feasible. (viii) Scientists studying WG regularly assess the causes of WG through retrospective analysis from symptom to cause, including case studies and surveys. The COA found a similar list of facts improperly ignored by

the Circuit: (1) the caustic nature of phosphoric acid; (2) phosphoric acid being a WG-triggering environmental factor or chemical; (3) the intensity and duration of exposure; (4) the area of exposure; (5) the textbook timing of the immunological response; (6) the incredible extent of the immune response; (7) the manifestation and duration of a classic WG symptom, sinusitis; (8) Walters' predisposition to WG; and (9) the support of scientific literature either directly or by analogy. (COA Op. at 9-10.) The COA found this case to be highly distinguishable from *Elher*, in which the expert based his opinion solely on his own personal beliefs. (COA Op. at 15.)

As a preeminent expert at the forefront of the scientific community for over forty years, Dr. Gershwin's opinions, methods, and analysis of the published literature set the standard for sound opinions in the scientific community. The COA easily recognized the ample scientific support for Dr. Gershwin's opinions and that those opinions were rationally derived from a sound foundation, including commonly used scientific methods. The COA correctly reversed the Circuit's use of an overly rigorous gatekeeping standard, which demanded definitive proof with uncontested evidence, and the Circuit's abuse of discretion in ignoring the plentiful facts and literature confirming the reliability of Dr. Gershwin's scientific methodology and analysis.

STATEMENT OF FACTS

I. Factual Background

Walters went to Defendants' dental office on October 20, 2010 to have a permanent crown seated on a tooth. (Teri Walters Dep. Tr., "TW Tr.," at 33:14-25, **Ex. 1**.) After the appointment concluded, she obtained what she believed to be whitening solution and refrigerated it until using it on February 11, 2011. (TW Tr. at 34:18-22, 36:4-6,14-17, 38:10-25, **Ex. 1**; Aff. of Teri Walters, "TW Aff.", ¶¶ 4-5, **Ex. 2**.) The receptionist actually provided Walters with an etching solution called "Ultra-Etch." (TW Aff. ¶ 6, **Ex. 2**; TW Tr. at 46:1-2,8-14, **Ex. 1**.)

Defendants state that "[u]nder no circumstances is etching solution ever dispensed to a

patient. It is not intended for individual patient use." (Defs.' Resp. to Pls.' First Interrogs. And Reqs. to Admit., "Resp. 1st Interrogs.-Admit.," Interrog. 18, **Ex. 3**.) They admit that use of etching solution would require cosmetic repair "if there was severe damage to the enamel over an extended period of time." (Resp. 1st Interrogs.-Admit., Admit 8, **Ex. 3**.) Dr. Donald Falik confirmed that etching solution is made up of 35 percent phosphoric acid, which he indicates is a caustic acid and is not meant to be used for teeth whitening. (Dr. Donald S. Falik Dep. Tr., "DF Tr.," at 43:20-44:4, **Ex. 4**.) Dr. Robert Falik testified that the solution etches the teeth, and a little drop is left on the tooth for about 20 seconds only. (Dr. Robert C. Falik Dep. Tr., "RF Tr.," at 26:3-7, **Ex. 5**.) Dr. Donald Falik agreed that etching solution should only remain on the tooth for about 20 seconds and that the etching solution dissolves mineral from the tooth enamel and creates "literally miles of microscopic fingerlets" in the tooth. (DF Tr. at 45:20-46:10, **Ex. 4**.) Dr. Robert Falik also testified that etching solution can destroy a tooth if left on for a long period of time. (RF Tr. at 26:11-14, **Ex. 5**; *see also* Resp. 1st Interrogs.-Admit., Admit 8, **Ex. 3**.)

After sleeping with the solution in her mouth all night, Walters awoke with burning sensations inside her mouth, including along her gumline and the sides of her tongue. (TW Tr. at 43:3-25, 48:10-17, **Ex. 1**.) On April 5, 2011, Walters presented to Dr. David Luginbill's office complaining of sinus trouble that had been present for one month.[1] (Dr. Luginbill Progress Note, Dated Apr. 5, 2011, **Ex. 6**.) Dr. Luginbill performed a physical exam and noted that Walters's nasal areas were raw and swollen with nasal mucosa. (Dr. Luginbill Progress Note, Dated Apr. 5, 2011, **Ex. 6**.) Dr. Luginbill diagnosed Walters with "sinusitis." (Dr. Luginbill Progress Note, Dated Apr. 5, 2011, **Ex. 6**.) On April 14, 2011, PA Danielle Richards diagnosed Walters with acute sinusitis. (PA Richards Progress Note, Dated Apr. 14, 2011, at 2, **Ex. 7**.) On May 4, 2011, Walters presented to the office of Mid-Michigan Ear, Nose and Throat and was seen by Dr. Mark

[1] One month prior to April 5, 2011 is March 5, 2011. Teri Walters used the phosphoric acid approximately three weeks before March 5 on February 11.

Lebeda, ENT, at the request of Dr. Luginbill for chronic sinusitis. (Mid-Mich ENT Report, Dated May 4, 2011, **Ex. 8**.) Walters gave a history of pain and pressure involving her sinuses and "…a recent infection that has been present for about 45 days."[2] (Mid-Mich ENT Report, Dated May 4, 2011, **Ex. 8**.) Walters noted plugging and fullness in her left ear that had not resolved and indicated her symptoms started after using the wrong solution from her dentist. (Mid-Mich ENT Report, Dated May 4, 2011, **Ex. 8**.) In the Sparrow Hospital ICU, Walters underwent numerous diagnostic evaluations and invasive procedures to determine the nature of her medical condition. On June 3, 2011, the pulmonary service performed a catheter placement for the plasmapheresis, a process of withdrawing the entire blood supply and then transfusing the blood back into the patient. The preoperative diagnosis for this procedure was Wegener's granulomatosis and vasculitis. (Sparrow Hospital Operative Report, dated June 3, 2011.)

Dr. M. Eric Gershwin, testified that Walters' WG onset resulted from intense exposure to phosphoric acid etching solution in combination with a genetic predisposition to WG.

II. Procedural Background

Defendants took Dr. Gershwin's deposition on August 20, 2013. (Dr. M. Eric Gershwin Dep. Tr. at 1, **Ex. 9**.) Defendants then filed a motion *in limine*, dated September 3, 2013, to preclude Dr. Gershwin from testifying based upon the scientific reliability of his testimony. (Defs.' Mot. *in Limine* to Preclude Expert, Sept. 3, 2013, Cir. Ct. Dkt. Nos. 71-72.) Plaintiffs filed a brief in opposition to Defendants' motion *in limine*. (Pls.' Resp. in Opp. To Defs.' Mot. *In Limine* to Preclude, Cir. Ct. Dkt. No. 75, Sept. 13, 2013.) On October 2, 2013, the Court entered an order granting Defendants' motion for the reasons stated in the record. (Order Granting Defs.' Mot. in Limine, Oct. 2, 2013, Cir. Ct. Dkt. No. 91, **Ex. 10**.)

At the motion *in limine* hearing on September 19, 2013, the Circuit made a number of

[2] "About 45 days" prior to May 4, 2011 is mid-March 2011. Teri Walters used the phosphoric acid approximately one month before mid-March on February 11.

statements and findings relevant to this appeal. As to Dr. Gershwin's qualification as an expert, the Circuit determined that "there's no questioning this guy's qualifications," Dr. Gershwin is likely the "preeminent" expert, and "there's no question he's qualified" to act as an expert on the issues of WG and immunology. (Mot. *in Limine* Hrg. Tr., "Hrg. Tr.," at 20, Sept. 19, 2013, Cir. Ct. Dkt. No. 92, **Ex. 11**.) The Circuit also held that expert testimony on the WG issues would "clearly" assist the trier of fact. (Hrg. Tr. at 20, **Ex. 11**.)

The Circuit briefly mentioned the sufficiency of the facts or data that Dr. Gershwin relied upon, but the court only raised this consideration as a part of its analysis of the reliability of the principles and methods applied by Dr. Gershwin. (Hrg. Tr. at 20-21, **Ex. 11**.) The Circuit found that this is where it "ran into trouble" in admitting Dr. Gershwin's opinion. (Hr. Tr. at 20, **Ex. 11**.) Nowhere in the hearing transcript does the Circuit take issue with the sufficiency of Dr. Gershwin's awareness of Walters' experiences and medical condition. Instead, the Circuit's "trouble" was with the sufficiency of general facts and data in the scientific community regarding WG causation. (Hrg. Tr. at 20-36, **Ex. 11**.)

The Circuit expressed concern that (i) a large number of people could be exposed to a highly potent electrophilic solution, like Walters was exposed, but those people might not get WG and (ii) Dr. Gershwin believed this was not scientifically meaningful. (Hrg. Tr. at 23, 25, **Ex. 11**; Dr. Gershwin Tr. at 30 - 31, **Ex. 9**.) Dr. Gershwin had testified that, due to the rarity of genetic predisposition to WG, 100 people could be exposed to etching solution and not develop WG, so the absence of any effect on a particular test population has no probative value as to whether a highly potent electrophilic etching solution could initiate WG. (Dr. Gershwin Tr. at 30:25 – 31:13, **Ex. 9**.) The Circuit overlooked genetic predisposition and concluded that the lack of effect on a small test population somehow supported a finding of unreliability.

The Circuit also questioned whether Dr. Gershwin had properly differentiated between

different types of ANCA when testifying why ANCA, an antibody, is made relative to the onset of WG. (Hrg. Tr. at 30, **Ex. 11**.) Dr. Gershwin specified the *cytoplasmic* antigen inducing the ANCA related to WG. (Dr. Gershwin Tr. at 15:19 – 16:10, **Ex. 9**.)

The Circuit questioned whether connections between silica exposure and WG supported Dr. Gershwin's opinion that Walters' exposure to phosphoric acid caused the onset of WG. (Hrg. Tr. at 20, **Ex. 11**.) It discounted the value of WG studies of other chemicals because it could not find reference in the literature to phosphorous, phosphate, or phosphoric acid in fertilizers, solvents, pesticides, or other chemicals that have been linked to the onset of WG. (Hrg. Tr. at 24, 26-27, 29, **Ex. 11**.) Plaintiffs supplied to the Circuit and to this Court scientific literature with references to such chemicals containing or related to phosphorous and linked to WG onset.

In analyzing only four of the nine SBH factors used to evaluate cause, the Circuit held that Dr. Gershwin's analysis did not satisfy the temporality factor of the SBH test that inquires whether the cause preceded the effect. (Hrg. Tr. at 24-25, **Ex. 11**.) Despite acknowledging difficulty understanding Dr. Gershwin's testimony on this issue, the Circuit read Dr. Gershwin's testimony to state that Walters might have experienced the onset of WG independently of the phosphoric acid. (Hrg. Tr. at 25, **Ex. 11**.) Dr. Gershwin testified unequivocally that the onset of WG occurred in Walters because of the phosphoric acid, but he also responded to defense counsel's hypothetical question that generated confusion for the Circuit. (Dr. Gershwin Dep. Tr. at 34:15-23, **Ex. 9**.) Dr. Gershwin further testified that the phosphoric acid etching solution caused the autoimmune effects in Walters because of her genetic predisposition to WG, which was exhibited by an acute presentation of an abundance of ANCA. (Dr. Gershwin Dep. Tr. at 35:7-10, **Ex. 9**.) The court finally held that "[t]he problem [] for me is the cutting edge of medicine is simply not the standard for a courtroom." (Hrg. Tr. at 32, **Ex. 11**.)

On October 21, 2013, Plaintiffs moved for reconsideration of the order granting Defendants'

motion *in limine* to preclude Dr. Gershwin's testimony. (Pls.' Mot. for Recons. of Order Granting Defs.' Mot. *In Limine* to Preclude, Cir. Ct. Dkt. No. 95, Oct. 21, 2013.) On October 22, 2013, the Circuit entered an order denying Plaintiffs' motion for reconsideration. (Order Denying Pls.' Mot. for Recons., Oct. 22, 2013, Cir. Ct. Dkt. No. 96, **Ex. 12**.)

The COA heard the issue and reversed the Circuit in an opinion dated January 29, 2015. (COA Vacated Op. at 10, **Ex. 48**.) This Court vacated the COA opinion and remanded for reconsideration in light of *Elher*. (MSC April 25, 2016 Order, **Ex. 52**.) The COA accepted supplemental briefs and again reversed the Circuit in an opinion dated August 16, 2016. (COA Op. at 15, **Ex. 50**.) The COA held that the "trial court here made an error of law . . . by effectively requiring plaintiffs to establish causation and their case prior to trial and to do so definitively." (COA Op. at 11, **Ex. 50**.) The COA determined that the trial court failed to consider a variety of factual issues supporting Dr. Gershwin's analysis. (COA Op. at 11, **Ex. 50**.) The COA reviewed the medical information relating to Walters' condition, highlighting issues related the sinuses and nasal septum and passage. (COA Op. at 2-3.) The COA relied upon scientific literature describing the pathogenesis of WG consistent with Dr. Gershwin's testimony, including effects initially limited to the airways causing sinusitis for a period of months, and genetic predisposition combined with an environmental trigger, including inhaled agents such as phosphoric pesticides, fumes, particulates, silica, toxic substances, and solvents. (COA Op. at 3-5.) The COA found Dr. Gershwin's testimony consistent with the literature, including alteration of the mucosal airway by chemical agents such as solvents or pesticides, the mechanism of action involving incredibly electrophilic phosphoric acid exposed to water within the mouth, the chemical potency of phosphoric acid and the safety data sheet information, the analogy available between epidemiological data about other environmental factors sharing characteristics with phosphoric acid, the intensity and duration of exposure, the textbook

temporal immunological response, the acute onset with very high-titer ANCA, the classic sinus symptoms exhibited with WG onset, and an incredible inflammatory response resulting in WG onset. (COA Op. at 5-7.)

The COA addressed the *Chapin* analysis of MRE 702 and MCL 600.2955 (1) and evaluated the application SBH methodology within the context of that rule and statute. (COA Op. at 7-9.) The COA found nine factors underlying Dr. Gershwin's opinion were each reliably supported by the safety data sheet information and the peer-reviewed scientific literature: (1) the caustic nature of phosphoric acid; (2) phosphoric acid being an environmental factor capable of triggering inflammation consistent with WG onset; (3) the intensity and duration of exposure; (4) the area of exposure; (5) the textbook timing of the immunological response; (6) the incredible extent of the immune response; (7) the manifestation and duration of a classic WG symptom, sinusitis; (8) Walters' predisposition to WG; and (9) the support of scientific literature either directly or by analogy. (COA Op. at 9-11.) The COA emphasized that the literature established associations that were "probable," "likely," "consistent," "important," and "predominant," and that a definitively established causal link was not required. (COA Op. at 9-11.) The Circuit erred in requiring definitive proof of causation at the gatekeeping stage, and the Circuit erred in overlooking Dr. Gershwin's reliance upon the factors noted above that support his methods and opinion. (COA Op. at 11.) The COA found this situation analogous to *Chapin* and noted that in *Chapin*, studies actually showed no correlation between asbestos and mesothelioma, where there is no such negative showing between phosphoric acid and WG in the present case. (COA Op. at 12.) *Chapin v A&L Parts, Inc*, 274 Mich App 122, 135; 732 NW2d 578 (2007). On remand, the COA again reversed the Circuit, leaving the fact-finding role with the jury. (COA Op. at 12, 15.)

The COA carefully reviewed *Elher* and distinguished the *Elher* expert's reliance upon his own personal beliefs without any other support. (COA Op. at 12-13.) The COA identified

scientific literature submitted in *Walters* that indicates a connection between WG onset and exposure to toxic substances, including pesticides, which are often composed of phosphates, which is a salt or ester of phosphoric acid. (COA Op. at 13.) The COA identified support for Dr. Gershwin's opinion in Walters' symptomology and the progression of WG as well as the nature and danger of phosphoric acid combined with the circumstances of Walters' prolonged, oral exposure to the substance, the timing of the immune response, the chronology of events, the extent of the immune response, the presentation of classic WG symptoms, and Walters' predisposition to WG. (COA Op. at 13, 14-15.) Dr. Gershwin's opinion is not contradicted by, or inconsistent with, the scientific literature or the medical and chemical facts presented by Walters. (COA Op. at 14.) The COA found Dr. Gershwin's opinion to be supported by scientific analogy to similar substances in the scientific literature. (COA Op. at 14.) The COA concluded that "Dr. Gershwin's opinion was supported by myriad variables or factors," as opposed to the *Elher* expert's reliance purely upon his personal beliefs. (COA Op. at 15.)

ARGUMENT

The Circuit applied an inappropriate standard in interpreting and applying MRE 702 and MCL 600.2955(1) and improperly precluded Plaintiffs' expert witness from testifying on the life-shortening autoimmune disease, WG. The Circuit abused its discretion by ignoring substantial scientific support for the expert's opinions on WG and the commonplace nature of his methods of scientific analysis. The COA properly reversed the Circuit as a matter of law for applying an incorrect standard and for abuse of discretion for ignoring facts supporting the expert's reliability. The COA easily distinguished *Elher*, involving expert opinion based only on person beliefs, from *Walters*, involving support from scientific literature, medical and chemical facts, and a chronology of phosphoric acid exposure, WG symptoms, and a textbook immune response. Leave to appeal should be denied. Alternatively, the Circuit's analysis should be

rejected and the COA opinion affirmed. Dr. Gershwin's opinions are rationally derived from scientific articles and the application of respected SBH and retrospective analysis methodologies.

APPLICABLE STANDARDS OF REVIEW

A trial court's interpretation of evidentiary rules or statutes affecting the admissibility of evidence is an issue of law subject to *de novo* review. *Chapin*, 274 Mich App at 126 (citing *Waknin v Chamberlain*, 467 Mich 329, 332; 653 NW2d 176 (2002); *see also Mich DOT v Haggerty Corridor Partners Ltd P'ship*, 473 Mich 124, 133-134; 700 NW2d 380 (2005) (quoting *People v Lukity*, 460 Mich 484, 488; 596 NW2d 607 (1999) (holding that "whether a rule of evidence or statute precludes admissibility of the evidence" is a preliminary question of law subject to *de novo* review). A trial court's determination of whether to admit evidence is an issue subject to review for abuse of discretion. *Id*. A trial court's decision on a motion for reconsideration is also reviewed for an abuse of discretion. *Sherry v E Suburban Football League*, 292 Mich App 23, 31; 807 NW2d 859 (2011). An abuse of discretion exists when the "decision results in an outcome falling outside the range of principled outcomes." *Id*. (quoting *Barnett v Hidalgo*, 478 Mich 151, 158; 732 NW2d 472 (2007).

In *Elher*, this Court did not challenge the COA application of *de novo* review to the trial court's use of appropriate principles in its gatekeeping role. *Elher v Misra*, 308 Mich App 276, 288 (2014). Instead, this Court found an *abuse of discretion by the trial court* in applying an inapplicable "testing" factor but determined that the *complete lack of support for any other reliability factors* required the exclusion of the witness. *Elher*, at 14-16 (**Ex. 51**). This Court examined the evidence and provided a detailed analysis of whether the trial court's gatekeeping effort resulted in a principled outcome. *Elher*, at 2-5, 12-16 (**Ex. 51**).

LEGAL PRECEDENT

Ordinary negligence requires (1) a legal duty, (2) breach, (3) damages, and (4) proximate cause.

Hill v Sears, Roebuck & Co, 492 Mich 651, 660; 822 NW2d 190 (2012). Proximate cause for negligence is "well-settled" and requires both legal causation, or foreseeability, and cause-in-fact, or "but for" cause. *O'Neal v St John Hosp & Med Ctr*, 487 Mich 485, 496; 791 NW2d 853 (2010). Proximate cause is treated the same in medical malpractice and ordinary negligence cases. *Id*. There can be more than one proximate cause contributing to an injury, and all that is necessary is that the negligent act be "a proximate cause" of the injury rather than "the proximate cause." *Id*. at 496-97.

"The critical inquiry with regard to expert testimony is whether such testimony will aid the factfinder in making the ultimate decision in the case." *People v Coy*, 243 Mich App 283, 294-295; 620 NW2d 888 (2000). MRE 702 permits expert testimony under the following circumstances:

> If the court determines that scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education may testify thereto in the form of an opinion or otherwise if (1) the testimony is based on sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case. (MRE 702.)

In addition, the provisions of MCL 600.2955 should inform this Court's analysis of whether expert opinion is appropriate. That statutory section states in relevant part that,

> In an action for the death of a person or for injury to a person or property, a scientific opinion rendered by an otherwise qualified expert is not admissible unless the court determines that the opinion is reliable and will assist the trier of fact. In making that determination, the court shall examine the opinion and the basis for the opinion, which basis includes the facts, technique, methodology, and reasoning relied on by the expert, and shall consider all of the following factors:
>
> (a) Whether the opinion and its basis have been subjected to scientific testing and replication.
>
> (b) Whether the opinion and its basis have been subjected to peer review publication.
>
> (c) The existence and maintenance of generally accepted standards governing the application and interpretation of a methodology or technique and whether the opinion and its basis are consistent with those standards.
>
> (d) The known or potential error rate of the opinion and its basis.
>
> (e) The degree to which the opinion and its basis are generally accepted within the relevant expert community. As used in this subdivision, "relevant expert community" means individuals who are knowledgeable in the field of study and are gainfully employed applying that knowledge on the free market.
>
> (f) Whether the basis for the opinion is reliable and whether experts in that field would rely on the same basis to reach the type of opinion being proffered.

(g) Whether the opinion or methodology is relied upon by experts outside of the context of litigation. (MCL § 600.2955(1).)[3]

In evaluating the reliability of expert opinion, "the inquiry is flexible and focused 'solely on principles and methodology' rather than ultimate conclusions." *Chapin*, 274 Mich App at 127 (quoting *Daubert v Merrell Dow Pharmaceuticals, Inc*, 509 US 579, 594-95 (1993). A court's "role as gatekeeper does not require it to search for absolute truth, to admit only uncontested evidence, or to resolve genuine scientific disputes" even where there is conflicting evidence or opinions. *Id*. In the case of conflicts of evidence or opinion, the expert opinion is admissible "as long as the opinion is rationally derived from a sound foundation." *Id*. Section 600.2955(1) "does not require that each and every one of those seven factors must favor the proffered testimony." *Id*. at 137; *see also Elher*, at 13 and n 23, 14-15 (**Ex. 51**) (application of improper factors may be an abuse of discretion). "The standard focuses on the scientific validity of the expert's methods rather than on the correctness or soundness of the expert's particular proposed testimony." *People v Unger*, 278 Mich App 210, 217-18, 220; 749 NW2d 272 (2008). This distinction between reliable methods and debatable expert opinions is important because "not every particular factual circumstance can be the subject of peer-reviewed writing," and when unique facts arise, and there is not medical or scientific literature in support of an expert's conclusions, it is up to counsel to cross-examine the experts and it is up to the jury to determine which expert is more credible. *Id*. at 220. Where conflicting opinions of experts arise, it is a matter of credibility for the jury to resolve. *See Martin v Ledingham*, 488 Mich 987, 987-88; 791

[3] Defendants argue that "applying MCL 600.2955 (2), the trial court concluded that Dr. Gershwin's opinion and methodology were novel and new." (Defs' Br. at 8, 22.) However, the trial court never mentions MCL 600.2955 (2). Instead, the judge expressly stated that "I'm considering the rules set forth in MRE 702, the statute 600.2955 (1) and the case law." (Hrg. Tr. at 19, **Ex. 11**.) MCL 600.2955 (2) is not applicable. There is no "novel methodology or form of scientific evidence" at issue. Dr. Gershwin used the same method of tracking cause and effect shown in decades of peer-reviewed case control WG studies. (*See, e.g.*, **Exs. 18, 20, 21, 25, 26**.)

NW2d 122 (2010) (contrary expert opinions regarding standard of care created a jury question).[4]

In a motion for reconsideration, "[t]he moving party must demonstrate a palpable error by which the court and the parties have been misled and show that a different disposition of the motion must result from correction of the error." MCR 2.119(F)(3).

I. Dr. Gershwin's Opinions Are Based Upon Reliable Scientific Principles And Methods.

A. Qualified Expert

There is no dispute that Dr. Gershwin possesses the knowledge, experience, training, and education (MRE 702) in the matters of medicine and science at issue, including WG, immunology, rheumatology, and autoimmune disease; nor is there any dispute that expert opinion would assist the trier of fact. (*See* Hrg. Tr. at 20, **Ex. 11**; COA Op. at 11 & n 8.) Dr. Gershwin's extensive 107-page curriculum vitae ("CV") demonstrates significant relevant experience, training, and scholarly research and writing. (Dr. M. Eric Gershwin Curriculum Vitae, **Ex. 14**.) The CV lists Dr. Gershwin's multiple post-graduate degrees in medicine and science, his prestigious teaching, writing, and world and national health organization positions, his lifetime award in the field of autoimmunity, and recent discoveries of autoimmune disease environmental factors. (**Ex. 14** at 1-5.) The CV reflects Dr. Gershwin's prolific written and experimental contributions to autoimmune disease and rheumatology fields. (**Ex. 14** at 8-107.) In the 1970s, Dr. Gershwin performed clinical studies of Cyclophosphamide to treat WG and that drug is still used to treat WG today. (Dr. Gershwin Tr. at 11:17 – 12:10, **Ex. 9**.) He has written,

[4] In their Leave Application, Defendants attach the affidavit of Dr. Monika Mohan, who affirmed under oath that, "within a reasonable degree of medical certainty," Mrs. Walters' use of phosphoric acid etching solution "was not the cause of her" WG. (Defs.' Leave App., Ex. C, Aff. of Dr. Mohan ¶ 3.) Defendants' expert purports to have the ability to determine with medical certainty whether or not a particular factor caused WG in Teri Walters. Such conflict of expert opinions should be left for jury resolution so long as the experts have based their differing conclusions upon reliable methods of scientific inquiry. "The courts are not in the business of resolving scientific disputes." *Chapin*, 274 Mich App at 139. "The courts are unlikely to be capable of achieving a degree of scientific knowledge that scientists cannot." *Id.*

among other things, textbooks on sinus disease that address WG. Gershwin, M.E., *et al*., *Diseases of the Sinuses, A Comprehensive Textbook of Diagnosis and Treatment* (Humana Press, 1996, 2013) (cover page, **Ex. 15**). Indeed, the Department of Health and Human Services, National Institutes of Health has committed millions of dollars to research performed by Dr. Gershwin, including a recent award of over one and one-half million dollars over five years related to research of an autoimmune condition. (Nat.'l Inst. of Health, Notice of Award to M.E. Gershwin re *Xenobiotics and Primary Biliary Cirrhosis*, **Ex. 16**.)

B. Sufficient Facts or Data

The Circuit and the COA accepted the sufficiency of the facts or data relied upon. MRE 702. (Hrg. Tr. at 20-21, **Ex. 11**; COA Op. at 12.) Dr. Gershwin testified that he relied upon Walters' medical records and the case evaluation summaries and exhibits. (Dr. Gershwin Tr. at 18:11-13, **Ex. 9**.) Plaintiffs' case evaluation exhibits included, among other things, the etching solution "Safety Data Sheet"; information from Defendants' depositions, records, and correspondence; records from David Luginbill, D.O.; records from Douglas Hinterman, D.D.S.; records from David Golder, D.D.S.; records from Dr. Kara Hoisington, endocrinologist; records from Dr. Mark Lebeda, ENT; records from admission to Sparrow Hospital; Defendants' responses to various interrogatories; and Walters' affidavit. Therefore, there was no challenge the sufficiency of Dr. Gershwin's awareness of Walters' condition and experiences.

C. Reliable Principles and Methods Applied Reliably to the Facts

1. The Methodologies Applied

Dr. Gershwin's opinions are also the product of reliable principles and methods that he applied reliably to the facts of this case. Plaintiffs refer the Court again to *Chapin*, in which the issue was whether the expert was permitted to opine on the causal connection between disease and inhalation of brake dust containing asbestos. *Chapin*, 274 Mich App at 125. The COA

found that both MRE 702 and MCL 600.2955 (1) were satisfied despite the fact that experimentation was unavailable because "[i]t would, of course, be unethical to perform clinical experiments on people by deliberately exposing them to asbestos to confirm its toxicity, no matter how probative such an experiment might be." *Id*. at 127 and n2, 134. Instead, *the COA held that it was appropriate for the expert to rely upon the scientifically accepted SBH methodology for establishing causation*. *Id*. at 133-34. This methodology was relied upon by Dr. Gershwin, here, to analyze data and studies regarding the onset of WG caused by a variety of environmental triggers and then applying that information to the present case by analogy. (Aff. of Dr. M. Eric Gershwin, dated Sept. 16, 2013, ¶ 2, **Ex. 17**.[5]) Such reasoning by analogy is entirely appropriate under the recognized SBH criteria, and it is a necessary methodology where experimental testing would be unethical.

The nine SBH criteria include (1) strength of association, (2) temporality, meaning cause precedes effect, (3) biological gradient, meaning that generally the greater exposure leads to greater incidence of the effect, (4) consistency, meaning the effect is observed in multiple studies, (5) specificity, meaning a strong association between a specific agent and the same effect, (6) plausibility, meaning a plausible mechanism between cause and effect, (7) coherence, meaning a review of consistency between the theory and other theories of cause and effect, (8) experimental evidence, which refers to animal and laboratory studies, and (9) analogy, meaning the consideration of the effects of similar factors. *See, e.g., Chapin*, 274 Mich App at 134-35. Dr. Gershwin relied upon the SBH criteria in his testimony, without specifically mentioning the criteria, by explaining that scientific principles of analogy and mechanisms of action permit data and principles derived from peer-reviewed analysis to be applied to evaluate the effect of phosphoric acid in initiating WG symptoms. He emphasized the ethical problems with

[5] This affidavit was submitted to the Circuit and defense counsel on September 17, 2013 in support of Plaintiffs' opposition to Defendants' motion *in limine* to preclude Dr. Gershwin.

experimental testing in the context of WG, which necessitates the use of analogy to peer-reviewed studies of naturally occurring incidents of WG arising from exposure to a variety of substances. Dr. Gershwin's testimony regarding these matters is discussed fully below.

Dr. Gershwin's methodology meets the factors weighed in the SBH methodology for the following reasons: (1) The strength of association is high in this case because the acute onset of WG followed closely an intense exposure to phosphoric acid, which bears similar or more potent properties than substances such as silica, hydrocarbons containing phosphates, pesticides containing phosphates, and other chemicals studied in peer-reviewed articles presented. (2) Temporality exists as the WG symptoms, including sinusitis and more extreme respiratory distress, appeared after Walters' exposure to the phosphoric acid. (3) Biologic gradient is strong, given Walters' oral exposure to a caustic acid over several hours and the onset of WG devolved into very severe symptoms, rather than reaching only lesser WG symptoms, such as sinusitis.

(4) Consistency in effect is met because studies involving triggers of WG routinely include chemicals that share characteristics with phosphorous or contain phosphorous. (5) Specificity is less certain given the lack of experimental data showing exposure of phosphoric acid to patients genetically predisposed to WG, but the similarities to other chemical triggers referred to in factor (4) addresses the association between phosphorous and related chemicals to WG onset. Any experimental exposure to phosphoric acid would be highly unethical, as with the asbestos in *Chapin*. (6) Walters' oral exposure to phosphoric acid shortly before the onset of WG symptoms is consistent with an anticipated immunological response and demonstrates the existence of a plausible mechanism between cause and effect.

(7) Dr. Gershwin's opinion of WG causation from intense exposure to phosphoric acid is consistent with peer-reviewed studies of WG triggered by chemicals demonstrating similar key properties or being substantially composed of phosphorus, and substantiates the requisite

coherence. Dr. Gershwin notes that the analogous chemicals, such as silica, phosphorus based hydrocarbons, phosphorus based pesticides, and other types of solvents, are *much less chemically potent than the phosphoric acid* to which Walters was exposed. (8) Experimental evidence is not directly available. The studies and scholarly publications consistently show that the scientifically accepted approach is to locate patients with WG and to backtrack from the disease to the cause while accounting for variables in the environment. Human testing is unethical, and, as is discussed *infra*, animal testing is not currently effective in replicating the onset of WG. (9) Analogy is a key component of Dr. Gershwin's opinion in that he relies upon the studied effects of similar, but less potent, chemicals in causing the onset of WG.

Because experimental testing is unavailable, Dr. Gershwin relied upon a retrospective analysis of factors to determine the cause of WG onset in Walters. Dr. Gershwin pointed out that the literature looks backward from the WG case to proposed environmental causal factors and that he relied upon scientific analogy to other studies of WG causes and upon the mechanisms of action initiating the disease. (Dr. Gershwin Tr. at 23:21 – 24:11.) Walters presented with an acute onset of WG, showing high levels of ANCA, following a prolonged, intense exposure to phosphoric acid. (Dr. Gershwin Tr. at 26:3-11.) The timing of Walters' WG onset following her use of the phosphoric acid was a perfect primary immune response and the timing and scope of her symptoms occurred precisely as an immunology textbook would predict. (Dr. Gershwin Tr. at 263:23 – 27:8.) Dr. Gershwin further explained that Walters' crescendoing respiratory distress allowed him to trace the immune response back, like "a footprint or a fingerprint," to her intense oral exposure to the highly electrophilic phosphoric acid a few weeks earlier. (Dr. Gershwin Tr. at 27:9 – 28:11, 32:17-22.) This "backtracking" of the primary immune response and other factors is necessary because of the inability to perform experimental testing. (Dr. Gershwin Tr. at 35:5 – 37:14.) Dr. Gershwin relied on the phosphoric acid Safety Data Sheet, the timing of

Walters' clinical presentation, and data available on environmental factors associated with WG to determine the cause of WG in Walters. (Dr. Gershwin Tr. at 29:25 – 30:4.)

Dr. Gershwin's method of backtracking from known factors and time frames toward the cause of WG is a commonly accepted causation methodology. A 2006 study by Alfred Mahr evaluates WG causes by analyzing hospital patients exhibiting WG and surveying the general population in order to "identify the determinants of disease occurrence," including genetic and environmental risk factors. Mahr, A.D., Neogi, T., and Merkel, P.A., *Epidemiology of Wegener's granulomatosis: Lessons from descriptive studies and analyses of genetic and environmental risk determinants* (Clinical and Experimental Rheumatology 24 (Suppl. 41) 2006), at S-82-88 (see highlighted passages; quote at S-86) (**Ex. 18**). The Mahr article demonstrates the acceptance of studying WG backward from effect to cause through surveys, observation of WG patients, demographic assessments, retrospective case-control studies, examination of occupational exposure to various substances, and other descriptive and analytical review of data not involving experimental testing. *Id*. In a study by Suzanne Lane, the authors recognized an association between inhaled fumes, particulates, and pesticides with the onset of WG in contrast to healthy control subjects or control subjects suffering from rheumatism. Lane, S., Watts, R., and Scott, D., *Epidemiology of Systemic Vasculitis* (Curr. Rheumatology Reports, Vo. 7, 2005), at 272 (**Ex. 20**). The authors discussed their own findings regarding the causes of WG in various patients based upon retrospective analysis and concluded that comparison of population data over time, between geographic areas, and between different populations, is important in finding WG causes. *Id*. at 274. This reinforces the scientific community's methodology of tracing WG effects back to environmental and genetic causal factors.

The general acceptance of Dr. Gershwin's analysis backward from effect to the cause of WG is further supported by a meta-study by Young Ho Lee that examined nine studies comparing

1,922 vasculitis patients to 11,505 normal control subjects in order to determine whether a particular phosphate-linked polymorphism created genetic susceptibility to vasculitis and WG. Lee, Y.H., *et al*., *The protein tyrosine phosphatase nonreceptor 22 C1858T polymorphism and vasculitis: a meta-analysis* (Mol Biol Rep, ed. 39, 2012), at 8505-06 (**Ex. 21**). Based upon the review of comparative studies between healthy subjects and those with disease, the authors determined that the phosphate-linked polymorphism is a gene associated with susceptibility to WG. *Id*. at 8510. Thus, scientists studying WG rely upon retrospective analysis of patients to distinguish both environmental and genetic factors resulting in the onset of WG. *See also* Lane, S., Watts, R., *et. al*, *Are Environmental Factors Important in Primary Systemic Vasculitis?* (Arthritis & Rheumatism, Vol. 48. No. 3, 2003), at 814-17, 820 (performing a study with a "retrospective design" that presented a structured questionnaire to vasculitis patients and control subjects and found significant association between farming and WG which was consistent with a Duna report linking pesticides and insecticides to WG onset) (**Ex. 25**); Duna, G.F., Cotch, M.F., *et. al*, *Wegener's granulomatosis: Role of environmental exposures* (Clinical and Experimental Rheumatology, Vol. 16, 1998), at 669 (examining the etiology of WG through questionnaires to WG patients, healthy control subjects, and others and finding statistically significant results regarding WG patients' vocational exposure to fumes or particulate materials) (**Ex. 26**). Thus, scientific literature supports Dr. Gershwin's method of retrospectively analyzing Walters' clinical presentation, the phosphoric acid Safety Data Sheet, the timing of WG onset and symptoms, and available data on associated substances linked to the onset of WG, to draw his conclusion that intense exposure to phosphoric acid caused WG onset in Walters.

Retrospective analysis has been approved as a reliable method upon which to base expert opinion in other cases where the disease or condition could not be subjected to testing or prediction. In *Robelin v Spectrum Health Hosps*, 488 Mich 1000, 1001-02 (2010) (Kelly, C.J.

concurring), Chief Justice Kelly recognized that an expert's basic methodologies and principles must be sound and held that retrospective analysis of data is sufficient to support an expert opinion that hypoxia caused a neonatal stroke even though the experts agreed there are no known predictors of or prospective tests for neonatal strokes. This Court chose not to overrule a COA decision holding that the expert's retrospective use of the well-known process of elimination was sufficient to support his opinion that hypoxia is associated with and caused neonatal stroke, which conclusion was drawn in no published scientific literature. *Robelin v Spectrum Health Hosps*, unpub'd op *per curiam* of the Court of Appeals, issued Sept 10, 2009 (Dkt. No. 279780); 2009 Mich App LEXIS 1865 at *12-15 (**Ex. 46**). While neither prenatal hypoxia nor WG can be prospectively tested to determine the factors and causes of its onset and development, experts should be permitted to identify scientific and medical evidence and work backward from the effect to identify a cause even where expert's proposed cause may be subject to debate.

Cause has been traced backward from effect in the area of cancer onset and development. In *Clerc v Chippewa County War Mem Hosp*, unpub'd op *per curiam* of the Court of Appeals, issued Nov 14, 2013 (Dkt. No. 307915); 2013 Mich App LEXIS 1823, at *16-21, 35-36 (**Ex. 47**), the COA found that "backward staging" of cancer progression based upon conditions presently identified was an accepted technique and sufficient to permit an expert's opinion of the plaintiff's condition at a point prior to diagnosis. The Court noted cancer progression is not subject to testing because no physician could ethically request a patient to abstain from treatment in order to examine the development of untreated cancer over time and no patient would willingly offer to go untreated for such a purpose. *Id*. at 17-18. The COA reaffirmed that an expert's conclusions need not be supported by peer-reviewed literature and that following a methodology supported by scientific literature, such as backward staging, is sufficient to allow the expert's opinions to reach a jury. *Id*. at *18-21, 35-36. As in *Robelin* and *Clerc*, Dr.

Gershwin has applied an approach endorsed within the scientific literature of proceeding backward from the point of diagnosis to analyze the patient's condition at an earlier time. In each situation, the expert was dealing with a condition that could not be tested prospectively to confirm cause in effect. In each case, the experts employed retrospective analysis, based upon the patient's present medical conditions, other known factual conditions, and reliance upon a body of scientific knowledge, to trace the disease backward in time to its cause and development.

Because retrospective analysis and the SBH methodology are commonly employed to examine the causes and development of WG and other conditions that cannot be proactively tested, the Circuit below erred in excluding Dr. Gershwin as an expert. His methods of analysis are reliable in the scientific community, so his opinion should reach the jury even if his conclusions are subject to debate and cross-examination by Defendants and their experts. The detailed discussion below further establishes that Dr. Gershwin's analysis is consistent with the scientifically accepted SBH and retrospective analysis methodologies for establishing cause.

2. WG Requires A Rare Genetic Predisposition

Dr. Gershwin opined that the onset of WG is based, in part, upon a rare genetic predisposition, which makes it a highly uncommon disease. (*See*, *e.g.*, Dr. Gershwin Tr. at 7:23 - 8:5, 16:19 - 17:3, 23:2-8, 30:25 – 31:13, **Ex. 9**.) *See* Mahr, Neogi and Merkel, *Epidemiology of Wegener's granulomatosis*, *supra*, at S-82, S-86-88 (stating that the rate of incident of WG is between 3 and 14 per million annually and that WG is the product of genetic and environmental factors, such as silica, organic solvents, fumes, and pesticides) (**Ex. 18**); Hamidou, M., Audrain, M., *et. al*, *Staphylococcus aureus, T-cell repertoire, and Wegener's granulomatosis* (Joint Bone Spine, 68:373-77, 2001), at 373 (stating pathogenesis of WG involves genetic susceptibility and environmental factors, including "toxic substances (silica)," among other things) (**Ex. 19**); Lane, S., Watts, R., and Scott, D., *Epidemiology of Systemic Vasculitis*, *supra* at 272 (stating that

genetic predisposition is insufficient to trigger WG absent environmental factors) (**Ex. 20**).

Dr. Gershwin testified that 100 people could be exposed to etching solution and not develop WG. The genetic predisposition to WG is so rare that it is likely no one in the test population would develop WG even with an appropriate triggering agent. (Dr. Gershwin Tr. at 30:25 – 31:13, **Ex. 9**.) The Circuit expressed concern that people could be exposed to a highly potent electrophilic solution but those people might not develop WG. (Hrg. Tr. at 23, 25, **Ex. 11**; Dr. Gershwin Tr. at 30 - 31, **Ex. 9**.) That concern stemmed from the Circuit's failure to consider the well-supported conclusion that WG requires a rare genetic predisposition. Instead, the court erroneously assumed that a caustic, electrophilic solution is not a reliable trigger for Walters' WG onset because the chemical might not trigger WG in many subjects.

Failure to properly analyze genetic predisposition in the onset of WG caused the court to erroneously draw a distinction between the reasoning applied in *Chapin*, 274 Mich App 122, and to reject the reliability of Dr. Gershwin's opinions on WG. The Circuit noted that in *Chapin*, the court determined that asbestos affects all people the same way, and the Circuit contrasted that with its misunderstanding of Dr. Gershwin's testimony that any number of people could be exposed to electrophilic solutions without developing WG. (Hrg. Tr. at 23, **Ex. 11**.) Asbestos-related diseases are not premised upon *genetic predisposition*, while WG only afflicts those with a genetic predisposition. Consequently, the Circuit minimized the reliability of Dr. Gershwin's opinion by improperly comparing a non-genetic disease to a genetic disease. The real value of *Chapin* is not in comparing asbestosis to WG but in analyzing reliable methods of studying disease causes where experimental testing is impossible and/or unethical. One such method is to examine causes of disease using the SBH criteria.

The requirement of genetic predisposition for the expression of WG is supported in the scientific literature. A meta-study performed in 2012 examined nine underlying studies

involving 1,922 vasculitis patients and 11,505 control subjects. Lee, Y.H., *et al*., *The protein tyrosine phosphatase nonreceptor 22 C1858T polymorphism and vasculitis: a meta-analysis*, *supra* at 8505 (**Ex. 21**). Such a meta-study integrates the findings of numerous independent studies. The Lee meta-study focused on a particular polymorphism, or a distinct form, of the protein tyrosine phosphatase nonreceptor 22 gene and its contribution to the genetic susceptibility to ANCA-associated vasculitis and to WG. *Id*. at 8505, -8506. "Phosphatase" is an enzyme that removes a phosphate group from its substrate in a process that involves, among other things, phosphoric acid. The conclusion of the Lee meta-study is that this phosphatase-based gene and the particular polymorphism were associated with susceptibility to WG and "importantly contributes to autoantibody-related autoimmune diseases." *Id*. at 8510. While the introduction of the Lee meta-study indicated that the etiology of vasculitis is not "fully understood," the findings of the study should not be undervalued. *Id*. at 8506. That is, a polymorphism and gene linked directly to the chemical manipulation of phosphorous at the genetic level were shown to be associated with genetic susceptibility to WG and contributed to such autoantibody-related autoimmune diseases. *Id*. at 8505-06, 8510. Thus, this meta-study of other studies supports the reliability of the genetic predisposition component of Dr. Gershwin's opinion on WG causation and supports the reliability of Dr. Gershwin's opinion that phosphoric substances were critical to the onset of WG in Walters.

3. WG Involves Inflammation of the Upper Airways

Dr. Gershwin also stated his opinion that WG begins with the acute inflammation of the upper airways. (*See*, *e.g.*, Dr. Gershwin Tr. at 12:22-24, 14:17 – 15:8, 15:22 - 16:10, 33:14-17, **Ex. 9**.) *See* Hamidou, M., Audrain, M., *et. al*, *Staphylococcus aureus, T-cell repertoire, and Wegener's granulomatosis* (Joint Bone Spine, 68:373-77, 2001), at 373-74 (addressing WG and stating that in "the first phase, the disease is confined to the airways, causing sinusitis, ... The

second phase starts when the disease extends to other organs"; noting "general agreement" that the onset of WG involves the release of proteins signaling the body to generate an inflammatory response) (**Ex. 19**); *See* Mahr, Neogi and Merkel, *Epidemiology of Wegener's granulomatosis*, *supra*, at S-87 (recognizing the "commonly prominent airway disease seen in WG") (**Ex. 18**); Duna, G.F., Cotch, M.F., *et. al, Wegener's granulomatosis: Role of environmental exposures*, *supra* at 669, 673 (acknowledging the "predominant involvement of the airways" in the genesis of WG, and finding in a study that WG patients frequently reported inhalation of substances, and that this may trigger the onset of WG, involving "immuno-inflammatory events") (**Ex. 26**). Dr. Gershwin testified that the phosphoric acid etching solution has a chemical potency beyond any available comparisons and that it led to an "incredible inflammatory insult" to Walters. (*See, e.g.*, Dr. Gershwin Tr. at 29:7-12, **Ex. 9**.) The "Safety Data Sheet" for the Ultradent phosphoric acid etching solution supports this inflammatory activity by stating dangers of "permanent tissue damage," "corrosive, causes skin burning," "harmful if swallowed," "irritating to respiratory system," and by listing as "conditions to avoid" the "exposure to moist air or water," and by describing the hydrocarbon byproducts "phosphine" and "oxides of phosphorous" as "hazardous decomposition products." (Safety Data Sheet at 1-2, **Ex. 22**.)

Dr. Gershwin stated his opinion that exposure of the mucosal airway to various environmental factors and chemicals, which are related to the phosphoric acid etching solution here, create a higher risk of initiating WG. (*See, e.g.*, Dr. Gershwin Tr. at 8:5-9, 8:22 - 9:2, 21:21-25, **Ex. 9**.) Dr. Gershwin submitted a peer-reviewed publication providing a visual model of the onset of WG initiated by inflammation that activates neutrophils to release antigens resulting in the high level of "ANCA" (certain antibodies), and the article discusses environmental factors for the inflammation that include "infections, silica, drugs, etc." Chen, M. and Kallengberg, C., *The environment, geoepidemiology and ANCA-associated vasculitides*

(Autoimmunity Reviews ed. 9, 2010), at A293, A296 and Fig. 1 (**Ex. 23**). The Circuit questioned whether Dr. Gershwin had properly differentiated between different types of ANCA when testifying why the ANCA, an antibody, is made. The Court did note uncertainty about its analysis. (Hrg. Tr. at 30, **Ex. 11**.)

ANCAs are "anti-neutrophil cytoplasmic antibodies." Sibelius, U., *et al*., *Wegener's Granulomatosis: Anti-proteinase 3 Antibodies Are Potent Inductors of Human Endothelial Cell Signaling and Leakage Response* (J. Exp. Med., Vol. 187, No. 4, Feb. 16, 1998), at 497 (**Ex. 24**). Cytoplasmic ANCA (c-ANCA) is a seromarker of WG that is 95 percent specific to WG. *Id*. Proteinase 3 (PR3) is the target of the c-ANCA, meaning it is the substance that the antibody c-ANCA attacks. *Id*. In response to inflammation, neutrophils manifest PR3, which is then targeted by c-ANCA. *Id*. The importance of the presence of c-ANCA is that it indicates the onset of WG and is involved in the progression of the disease. *Id*. at 497, 502. In layman's terms, upper respiratory inflammation caused by an environmental stimulant leads to neutrophils release of an antigen to which c-ANCA responds in an overabundance in genetically predisposed patients marking the presence of WG in 95 percent of patients.

Critically, the Sibelius article is consistent with Dr. Gershwin's testimony on the pathology of WG and the presence of a "cytoplasmic antigen," such as PR3, and that the antibody generated was ANCA. (Dr. Gershwin Tr. at 15:19 – 16:10, **Ex. 9**.) While the Circuit may have preferred that Dr. Gershwin describe the pathology of WG using terms more susceptible to a layman's understanding, Dr. Gershwin's testimony regarding the presence of ANCA directed toward a cytoplasmic antigen following inflammation is confirmed by the Sibelius article's description of cytoplasmic ANCA responding to a PR3 antigen. Dr. Gershwin's deposition statements, when juxtaposed to the scholarly literature (with a medical dictionary at hand), prove to be consistent with such published literature. Dr. Gershwin's visual model of the onset of WG

displayed the neutrophils releasing antigens and the response of "ANCA." Dr. Gerswhin characterized the antigens as "cytoplasmic antigens," which necessarily means that the antibody responsive to such an antigen is a cytoplasmic antibody, or c-ANCA. Consequently, Dr. Gershwin accurately described the pathology of WG arising from an ANCA response to a cytoplasmic antigen caused by respiratory inflammation.

Inflammation of the upper airways at issue here derived from Walters' exposure to phosphoric acid etching solution. The inflammatory effect and chemical activity of phosphorous depends upon its chemical nature and bond. Thus, phosphoric acid is highly reactive while the phosphorous in baking powder is inert. Similarly, sulfuric acid corrodes while sulfur in rotten eggs does not. The Safety Data Sheet for the phosphoric acid in this matter warned against exposure to moisture or water and listed dangers of permanent tissue damage, corrosion, burning of the skin, and *irritation to the respiratory system*, among other things. (Safety Data Sheet at 1-2, **Ex. 22**.) The capacity for inflammation and biological injury from phosphorous is clear based upon the articles cited *infra* regarding chemical weapons, kidney and liver damage, and "Phossy Jaw" bone necrosis from inhalation or medication. (*See infra*, § (C)(4).) WG is a disease of the airways and borne of inflammation. Phosphoric acid is a corrosive material capable of intense biological inflammation. The WG in Walters occurred within the time frame of a textbook autoimmune response following intense oral exposure to phosphoric acid inflaming the airways.

4. Analogy to Studied Chemicals Supports WG Causation By Phosphoric Acid

Dr. Gershwin explained that scientific principles of analogy and the mechanism by which WG is triggered permit the data and principles derived from peer-reviewed analysis and epidemiological studies of various chemicals to be analogized in determining if exposure to phosphoric acid etching solution, a highly potent electrophilic solution, could lead to the onset of WG here. (*See, e.g.*, Dr. Gershwin Tr. at 9:11-14, 16:20-23, 22:8-24, 23:8-13, 24:4-10, 24:24 -

25:2, 28:5-10, **Ex. 9**.) He testified that environmental factors studied in relation to the onset of WG include silica solvents and chemical solvents of all sorts that include a variety of electrophils. (*See, e.g.*, Dr. Gershwin Tr. at 26:14-18, **Ex. 9**.) *See* Lane, S., Watts, R., *et. al*, *Are Environmental Factors Important in Primary Systemic Vasculitis?*, *supra* at 814 (performing a case-control study through interviews using a structured questionnaire to groups including WG patients and finding WG associated with farming and high occupational solvent exposure) (**Ex. 25**). He emphasized that studies indicate silica to be a factor in the onset of WG, and silica shares important properties with phosphorus, including isoelectric focusing. (*See, e.g.*, Dr. Gershwin Tr. at 22:14-24, 23:8-13, **Ex. 9**.) *See* Hamidou, M., Audrain, M., *et. al*, *Staphylococcus aureus, T-cell repertoire, and Wegener's granulomatosis*, *supra*, at 373 (stating pathogenesis of WG involves environmental factors, including "toxic substances (silica)," among other things) (**Ex. 19**). Dr. Gershwin distinguished chemicals raised by the defense, such as peroxide, on the basis that they lack the electrophilic qualities and polarity present in phosphoric substances. (*See, e.g.*, Dr. Gershwin Tr. at 29:16-23, **Ex. 9**.)

As importantly, Dr. Gershwin testified that hydrocarbon solvents and pesticides previously evaluated in conjunction with the onset of WG contain phosphate and may be analogized to the potent phosphoric acid in this case. (*See, e.g.*, Dr. Gershwin Tr. at 22:21 - 23:3, 24:5-11, 24:22-23, **Ex. 9**.) Notably, the decomposition byproducts of the phosphoric etching solution here include hydrocarbons "phosphine" and "oxides of phosphorous." (Safety Data Sheet at 1-2, **Ex. 22**.) Peer-reviewed literature supports the causal link between these analogous hydrocarbons and pesticides with the onset of WG.[6] *See* Mahr, Neogi and Merkel, *Epidemiology of Wegener's*

[6] Scientific literature establishes that pesticides are most commonly made of phosphorous, which strengthens the analogy to the highly potent phosphoric acid here. *See* Betteridge, D., Thompson, M., Baker, A.D., and Kemp, N.R., *Photoelectron Spectra of Phosphorus Halides, Alkyl Phosphites and Phosphates, Organo-Phosphorus Pesticides, and Related Compounds* (Analytical Chemistry, Vol. 44 No. 12, 1972), at 2005 (addressing prevalence of pesticides

granulomatosis, *supra*, at S-82, S-86-88 (stating that WG is the product of environmental factors, such as silica, organic solvents, and pesticides) (**Ex. 18**); Duna, G.F., Cotch, M.F., *et. al*, *Wegener's granulomatosis: Role of environmental exposures*, *supra* at 669, 673 (finding statistically significant the onset of WG after exposure to fumes or particulate materials, particulate materials from construction, and occupational exposure to pesticides) (**Ex. 26**); Lane, S., Watts, R., and Scott, D., *Epidemiology of Systemic Vasculitis*, *supra* at 272 (finding conflicting evidence linking systemic vasculitis, including WG, to occupational exposure to hydrocarbons, and significant association with farming) (**Ex. 20**). Thus, an abundance of scientific evidence, regarding less potent chemicals containing phosphorous or with similar properties that supports a conclusion that phosphoric acid as the cause of WG.

The Circuit debated the relevance of silica to Walters' exposure to phosphoric acid. (Hrg. Tr. at 20, **Ex. 11**.) Silica shares key characteristics with phosphoric acid relevant to the inflammation and process of WG onset. Shared characteristics include isoelectric focusing and electrophilic properties. The importance of electrophilic properties is supported by a peer-reviewed article co-authored by Dr. Gershwin that addresses electrophilic properties in the cause of autoimmune disease. (Gershwin, M.E., *et al*., *Electrophile-modified lipoic derivatives of PDC-E2 elicits anti-mitochondrial antibody reactivity* (Journal of Autoimmunity ed. 37, 2011), at 209-16 (**Ex. 30**.) Dr. Gershwin studied the effects of electrophilic agents, particularly acetaminophen or non-steroidal anti-inflammatory drugs, and found that for those who are genetically susceptible,

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containing phosphorous) (**Ex. 27**); GoodGuide, *Organophosphate Pesticides: Dialkyl Phosphate Metabolites* (Scorecard 2011), at 1 (stating pesticides containing phosphate account for about half of insecticides used in the United States and interfere with the nervous system of insects and humans) (**Ex. 28**); National Biomonitoring Program, *Organophosphorus Insecticides: Dialkyl Phosphate Metabolites* (United States Centers for Disease Control and Prevention, 2013), at 1 (stating that insecticides containing phosphorus account for a large share of all insecticides in the United States, including 70% of all insecticides in 2001, and acute high dose effects include neurological dysfunction, among other things) (**Ex. 29**).

prolonged exposure to electrophilic agents may initiate or enhance the process resulting in an autoimmune liver disease, primary biliary cirrhosis. (*Id*. at 209, 214, 216.)

Other literature confirms Dr. Gershwin's testimony that phosphorous forms highly electrophilic and reactive compounds. Husain, K., *Delayed Neurotoxicity of Organophosphorus Compounds* (J. of Environ. Immun. and Toxicology, Vol. 1, issue 1, Mar./Apr. 2013), at 14-15 (phosphoric compounds used in nerve agents in WWII and now in pesticides leading to 300,000 casualties and deaths annually) (**Ex. 31**); Metcalf, R.I., *et al*., *Meta-sulfurpentafluorophenyl Diethyl Phosphate and Meta-sulfurpentafluorophenyl N-methylcarbamate as Insecticides and Anticholinesterases* (J. Of Economic Entomology, Vol. 55, No. 3, June 1962), at 340 (describing the electrophilic nature of the phosphorus atom and the increased reactivity of the element in combination with substances bearing electron-attracting or donating properties) (**Ex. 32**).

Other peer-reviewed literature establishes overlapping characteristics and interchangeability of silica and phosphorous. One article establishes the competitive characteristics of silica and phosphorous by showing a solution containing silica would remove phosphorous from wastewater containing phosphorous. (Yamashita, T., *et al., Simultaneous removal of colour, phosphorus and disinfection from treated wastewater using an agent synthesized from amorphous silica and hydrated lime* (Environ Technol., ed. 34, 2013), at 1017, 1019, 1024 (**Ex. 33**). Literature also establishes that in the presence of silica, other compounds take on electrophilic properties. Smith, K., *et al*., *New Reagent Systems for Electrophilic Chlorination of Aromatic Compounds: Organic Chlorine-Containing Compounds in the Presence of Silica* (Dept. of Chemistry, Univ. College of Swansea, U.K., Dec. 1985), at 1155 (**Ex. 34**). Occupational Safety and Health Association has published information explaining that silica induces the activity of phosphorous molecules in autoimmune processes, particularly by activating phosphoinositide contained within immune cells called macrophages. Occupational

Safety and Health Association, *Occupational Exposure to Respirable Crystalline Silica – Review of Health Effects Literature and Preliminary Quantitative Risk Assessment* (Docket OSHA-2010-0034), at 234 (table of contents and excerpt, **Ex. 35**). Activation of phosphoinositide has been linked to the development of vascular injury in WG. (*See*, *infra*, same section, discussion of U. Sibelius article at 498, **Ex. 24**.) The electrophilic impact of both phosphorous and silica, as well as the capacity of silica to affect phosphorous-based autoimmune processes, makes WG studies of silica relevant to phosphorous in the context of WG. Dr. Gershwin was fully justified by these associations between silica and phosphorous in the literature in relying upon studies of silica and WG to support his opinions relative to phosphoric acid and WG onset.

Aside from silica, the Circuit disregarded the value of studies of other chemicals by stating that it could not find reference in the literature to phosphorous, phosphate, or phosphoric acid in fertilizers, solvents, pesticides, or other chemicals that have been linked to the onset of WG. (Hrg. Tr. at 24, 26-27, 29, **Ex. 11**.) However, the literature establishes that phosphorous is contained in the chemicals that have been linked to WG. Moreover, the phosphorous contained in such chemicals, particularly pesticides, has been shown to create significant biological injury. Indeed, autopsy evidence demonstrates that a dying WG patient's kidneys were attempting to dispel an overabundance of phosphorous. Furthermore, the literature shows that phosphorous is central to autoimmune responses, including the processes leading to WG injuries.

Plaintiffs have produced literature that affirms the importance of phosphorous in chemicals, such as pesticides, that have been linked to the onset of WG. The Centers for Disease Control and Prevention (CDC) reports that a large share of all insecticides used in the United States are *organophosphorous* chemicals, people are exposed to these phosphoric chemicals by eating foods treated with the chemicals, and sudden exposure to large amounts of such chemicals may lead to breathing difficulty, paralysis, and seizures, among other crisis responses. *See*

Organophosphorus Insecticides: Dialkyl Phosphate Metabolites (United States Centers for Disease Control and Prevention, 2009), at 1 (**Ex. 36**); *see also* Petty, C.S., *et al.*, *Organic Phosphate Insecticides – A Survey of Blood Cholinesterase Activity of Exposed Agricultural Workers in Louisiana, 1957* (Am. J. Public Health, Vol. 49, No. 1, Jan. 1957), at 62 (discussing the use of organic phosphate insecticides and the toxicity of the substances) (**Ex. 37**). The literature confirms Dr. Gershwin's contention that phosphoric substances, including insecticides that have been associated with WG onset, are electrophilic in nature. Metcalf, R.I., *et al*., *Meta-sulfurpentafluorophenyl Diethyl Phosphate and Meta-sulfurpentafluorophenyl N-methylcarbamate as Insecticides and Anticholinesterases* (J. Of Economic Entomology, Vol. 55, No. 3, June 1962), at 340 (describing the electrophilic nature of the phosphorus atom and its usefulness in insecticides) (**Ex. 32**). The studies associating WG onset with pesticides are relevant to the phosphoric acid here because phosphates are widely used in pesticides. Blanc-Lapierre, A., *et al*., *Cognitive Disorders and Occupational Exposure to Organophosphates: Results From the PHYTONER Study* (Am. J. of Epidemiology, Vol. 177, No. 10, 2013), at 1086 (**Ex. 38**) (recounting the wide use of organophosphates in pesticides starting in the 1970s).

Organo*phosphorous* pesticides are used widely in agriculture, industry, and medicine. Wang, H.P., *et al*., *H NMR-based metabonomic analysis of the serum and urine of rats following subchronic exposure to dichlorvos, deltamethrin, or a combination of these two pesticides* (Chemico-Biological Interactions, Vol. 203, 2013), at 588 (**Ex. 39**). The Wang article analyzes effects of such pesticides on rats and concludes that the pesticides damage the kidneys or liver function in rats. *Id*. at 588, 595. Thus, phosphorous is used widely, particularly in pesticides, and has been shown to cause significant biological injury to tested animals.

Other literature establishes the highly electrophilic and reactive characteristics of phosphorous compounds and that such compounds were used as *chemical weapons* prior to

World War II and then in pesticides for gardening and agriculture and in flame retardants, synthetic resins, the polymer industry, and other uses. Husain, K., *Delayed Neurotoxicity of Organophosphorus Compounds* (J. of Environ. Immun. and Toxicology, Vol. 1, issue 1, Mar./Apr. 2013), at 14-15 (**Ex. 31**). The use of phosphorous compounds created a toxicity risk for non-target organisms and workers in a variety of occupations resulting in intoxications estimated at three million per year, with 300,000 deaths or casualties each year, from pesticide exposure. *Id*. Another article exposed the role of phosphorous exposure through modern medication or occupational inhalation during the early 1900s in causing "Phossy Jaw," or the exposure and necrosis of bone, particularly in the jaw. Marx, R., *Uncovering the Cause of "Phossy Jaw" Circa 1858 to 1906: Oral and Maxillofacial Surgery Closed Case Files—Case Closed* (Am. Assoc. of Oral and Maxillofacial Surgeons, 2008), at 2356, 2362-63 (**Ex. 40**). These articles underscore the capacity of phosphorous, including phosphoric pesticides, to cause severe biological injury and inflammation, *which is central to WG onset*.

Phosphorous has also been linked directly to WG. An article by Fred Sanfilippo recounts the discovery of abnormal calcium and phosphorous deposits on a membrane of the kidneys associated with WG during the autopsy of a man that had biopsy evidence of WG thirty months before his death. Sanfilippo, F., *et al*., *Crystalline Deposits of Calcium and Phosphorus* (Arch. Pathol. Lab. Med., Vol. 105, Nov. 1981), at 594, 596, 598 (**Ex. 41**). The WG patient's death was attributed to immunosuppressive therapy, among other things. *Id*. While the researchers in the Sanfilippo article could not determine the cause of the phosphorous and calcium deposits, the article provides documented evidence of a body's attempt to excrete unusual levels of phosphorous in a WG patient and supports the connection between phosphorous and WG. *Id*.

Dr. Gershwin's opinion that exposure to the highly electrophilic phosphoric acid initiated an autoimmune response triggering WG onset is supported by research showing phosphorous to be

at the center of immune responses. In a study by Aurelie Thedrez, researchers explained that certain human T cells, which produce inflammation, boost other immune responses, and kill antagonistic cells such as tumors, are broadly reactive because they respond to phosphorous-based antigens (phosphoantigens). Thedrez, A., *et al*., *IL-21-Mediated Potentiation of Antitumor Cytolytic and Proinflammatory Responses of Human Vγ9Vδ2 T Cells for Adoptive Immunotherapy* (The J. of Immunology, 2009), at 3423 (**Ex. 42**). As addressed *supra*, an article by Ulf Sibelius explains the pathology of WG in that the seromarker for WG, c-ANCA, targets a particular substance, PR3, that is produced by neutrophils in response to inflammation. Sibelius, U., *et al*., *Wegener's Granulomatosis: Anti-proteinase 3 Antibodies Are Potent Inductors of Human Endothelial Cell Signaling and Leakage Response* (J. Exp. Med., Vol. 187, No. 4, Feb. 16, 1998), at 497, 502 (**Ex. 24**). The PR3 produces alterations to endothelial cells, which cells create a thin, smooth layer of cells in the heart and blood vessels. *Id*. at 498. The PR3 alterations result in "pronounced activation" of phosphoinositide hydrolysis processes, related to the introduction of phosphates into organic molecules, that "may contribute to the development of vascular injury in WG." *Id*. at 498. Silica also works to induce the activity of phosphoinositide in immune cells. *See supra*, Occupational Safety and Health Association, *Occupational Exposure to Respirable Crystalline Silica – Review of Health Effects Literature and Preliminary Quantitative Risk Assessment* (Docket OSHA-2010-0034), at 234 (table of contents and excerpt, **Ex. 35**). In combination with the Thedrez and OSHA articles substantiating the central importance of phosphorus in effecting immune response, the Sibelius article adds support for the importance of phosphorous in the development of WG.

Defendants' internet article states that "Phosphoric acid is produced from phosphates by reacting with sulphuric acid" to suggest that none of the epidemiological studies are relevant to phosphoric acid. (Defs' Br. at 20 n1.) One of Plaintiffs' articles addresses the combination of

sulfur and phosphates in insecticides. Metcalf, R.I., *et al*., *Meta-sulfurpentafluorophenyl Diethyl Phosphate and Meta-sulfurpentafluorophenyl N-methylcarbamate as Insecticides and Anticholinesterases* (J. Of Economic Entomology, Vol. 55, No. 3, June 1962) (**Ex. 32**). Other articles establish the statistically significant association between pesticides, insecticides, fumes, particulates, and WG onset.[7] Lane, S., Watts, R., *et. al, Are Environmental Factors Important in Primary Systemic Vasculitis?* (Arthritis & Rheumatism, Vol. 48. No. 3, 2003), at 814-15, 820 (**Ex. 25**); Duna, G.F., Cotch, M.F., *et. al*, *Wegener's granulomatosis: Role of environmental exposures* (Clinical and Experimental Rheumatology, Vol. 16, 1998), at 669 (**Ex. 26**). The Court recognized the importance of such literature in its prior opinion. (COA Op at 4-5, 11.)

The Circuit missed such connections, stating it could not "find a reference to phosphorus, phosphate or phosphoric acid; or for that matter, any kind of acid" in the literature submitted by Dr. Gershwin.[8] (Hrg. Tr. at 24, 26, also 27 (no articles re acid), 29 (no articles re "chemicals, solvents and pesticides"), **Ex. 11**.) The Circuit overlooked articles submitted by Dr. Gershwin relative to pesticides, insecticides, particulates, and fumes. One of the overlooked articles specifically addresses "acid phosphatase," which has been associated with the initiation and relapse of WG, and notes that antibodies to the acid phosphatase are present in WG patients. Chen, M. and Kallengberg, C., *The environment, geoepidemiology and ANCA-associated vasculitides* (Autoimmunity Reviews ed. 9, 2010), at A293, A295 (**Ex. 23**).

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[7] Dr. Gershwin testified that WG is initiated by respiratory inflammation, and phosphoric acid produces incredible inflammation. (Dr. Gershwin Tr. at 12-14, 29, 33, **Ex. 9**.) The peer-reviewed literature states that WG is triggered by inflammation of the airways. (**Ex. 18** at S-87; **Ex. 19** at 373; **Ex. 26** at 669-70.) The safety data sheet states that phosphoric acid irritates the respiratory system. (Safety Data Sheet at 1, **Ex. 22**.) Walters *slept* with the acid in her mouth. These facts regarding inhaled substances are critical support for Dr. Gershwin's reliability.

[8] Defendants argued that "The trial court acknowledged that some testing involved a claimed connection with pesticides containing phosphates." (Defs' Suppl Br to COA at 10, citing Hrg. Tr. at 26-27.) The trial court actually said the opposite: "I looked for, and I think it's clear, there were no articles discussing phosphorus or phosphate exposure … phosphate and phosphorous are fairly common in terms of environmental factors. I mean, they're used in fertilizers … So I guess I was a little surprised that there weren't any." (Hrg. Tr. at 26, **Ex. 11**, emphasis added.)

In summary, phosphorous shares characteristics with substances linked to WG onset, phosphorous makes up substances linked to WG onset, phosphorous is capable of extreme biological trauma and inflammation that is a key step in the onset of WG, abnormal phosphorous levels were shown in the body of a deceased WG patient, and phosphorous plays a critical role in the body's immunological response that leads to WG. Either the Circuit interpreted too narrowly the relevant court rules and statute, or the Circuit abused its discretion in discounting the importance of such literature in establishing a scientific connection between phosphorous and WG and supporting the reliability of Dr. Gershwin's causation opinions.

5. The Mechanism of Action Supports Causation

Dr. Gershwin described the "mechanism of action" as the onset of sinus symptoms three to four weeks after intense exposure to phosphoric acid in water followed by upper airway issues and respiratory distress. He conducted a retrospective review of Teri Waters' condition from the point of the display of symptoms to a period several weeks before, as if one has found a footprint and is tracing the footprints back to their origin, which is the same process that led to the discovery of the cause of rheumatic fever. (*See*, *e.g.*, Dr. Gershwin Tr. at 27:9 - 28:11, 32:19-22, 33:14-25, **Ex. 9**.) Dr. Gershwin explained that Walters' sinusitis itself was not a cause of WG but a recognized symptom of WG that may manifest itself for years prior to the onset of the full WG syndrome. (*See*, *e.g.*, Dr. Gershwin Tr. at 32:3-19, **Ex. 9**.) Based upon the chemicals involved, the temporal proximity of symptoms to exposure, the high level of ANCA, the genetic predisposition to WG, the mechanism of action, the biologic plausibility, and comparable epidemiological studies, Dr. Gershwin opined that the phosphoric acid etching solution caused the onset of WG in Walters. (*See*, *e.g.*, Dr. Gershwin Tr. at 34:18 - 35:19, **Ex. 9**.) This backtracking from effect to cause is common in the study of WG and in other diseases that cannot be prospectively tested. (*See* discussion of scientific literature, *Chapin*, *Robelin*, and

Clerc, *supra* § (C)(1).)

Part of the mechanism of action addressed by Dr. Gershwin was the intensity of Walters' exposure to phosphoric acid. Dr. Gershwin explained that a high level of the antibody ANCA (antineutrophil cytoplasmic antibody) is indicative of WG. (*See*, *e.g.*, Dr. Gershwin Tr. at 15:5-6, 16:12-13, **Ex. 9**.) He testified that the high level of ANCA and the acute onset of WG in Walters from intense exposure to phosphoric acid were consistent with studies of silica exposure showing that the intensity of exposure, rather than duration of exposure, was most important in initiating WG. (*See*, *e.g.*, Dr. Gershwin Tr. at 26:2-11, 28:5-11, **Ex. 9**.) *See* Mahr, *et. al*, *Epidemiology of Wegener's granulomatosis*, *supra*, at S-87 (intensity of exposure is associated with WG onset more so than duration of exposure) (**Ex. 18**).

The timing of Walters' WG symptoms also supports Dr. Gershwin's opinion on causation and the mechanism of action. Dr. Gershwin noted that Walters' onset of WG symptoms occurred within three to four weeks of her use of the phosphoric acid etching solution on February 11, 2011. (*See*, *e.g.*, Dr. Gershwin Tr. at 26:23-25, **Ex. 9**.) The April 5, 2011 progress notes of Dr. Luginbill, reflect that Walters had been experiencing "sinus trouble" for one month and also presented with a "full ear" and irritation among other sinus effects. (Dr. Luginbill Progress Note, Dated Apr. 5, 2011, **Ex. 6**.) One month prior to April 5, 2011 is March 5, 2011, which is consistent with Dr. Gershwin's estimate that symptoms occurred three to four weeks after February 11, 2011. In a report by Mid-Michigan Ear, Nose & Throat relating to Walters' May 4, 2011 visit, Dr. Mark Lebeda wrote that Walters had been experiencing a sinus infection for approximately 45 days. (Mid-Mich ENT Report, Dated May 4, 2011, at 1, **Ex. 8**.) Forty-five days prior to May 4 is mid-March, which is approximately one month after Walters' exposure to the phosphoric acid and is consistent with Dr. Gershwin's testimony. The timing of Walters' WG response to the etching solution, manifested initially by sinus symptoms, was "absolutely

out of a textbook of immunology." (*See, e.g.*, Dr. Gershwin Tr. at 26:23 - 27:7, **Ex. 9**.)

Yet, the Circuit denied that Dr. Gershwin's analysis satisfied the temporality factor of the SBH test. (Hrg. Tr. at 24-25, **Ex. 11**.) The Circuit read Dr. Gershwin's testimony to state that Walters might have experienced WG onset regardless of the phosphoric acid. Significantly, it also remarked that it might be misunderstanding Dr. Gershwin's testimony. (Hrg. Tr. at 25, **Ex. 11**.) The Circuit committed an abuse of discretion in misinterpreting Dr. Gershwin's unwavering testimony that Walters's exposure to phosphoric acid etching solution triggered the onset of WG.

Defense counsel asked Dr. Gershwin at his deposition if it was Dr. Gershwin's opinion that "without the etching solution Mrs. Walters would not have developed Wegener's." (Dr. Gershwin Dep. Tr. at 34:15-17, **Ex. 9**.) This question was hypothetical in that it asked Dr. Gershwin to testify what would happen if Walters *was not* exposed to etching solution even though the facts as they exist establish that Walters *was* exposed to the solution. Dr. Gershwin gave the following response to defense counsel's subtle hypothetical question:

> Well, she wouldn't have developed Wegener's here at this time. I mean, I can say that she would not have got Wegener's had it not been for the etching solution. I can't say she wouldn't have gotten Wegener's in the future. It's possible. But she certainly wouldn't have got Wegener's at this moment. (Dr. Gershwin Dep. Tr. at 34:18-23, **Ex. 9**.)

The Court appears to have misinterpreted this testimony as meaning that Walters may have presently developed WG regardless of the etching solution. Dr. Gershwin reaffirmed that the reason for the onset of WG in this case is that Walters was exposed to phosphoric acid etching solution. (Aff. of Dr. M. Eric Gershwin, dated Oct. 17, 2013, ¶ 1, **Ex. 43**.) Dr. Gershwin clarified to the Circuit that the remainder of his testimony was in response to the hypothetical nature of defense counsel's question about what might have happened to Walters *without* being exposed to etching solution. (Dr. Gershwin Aff., dated Oct. 17, 2013, ¶ 1, **Ex. 43**.) Dr. Gershwin's testimony was and is that some other environmental factor in the future might have triggered

WG if Walters had hypothetically never developed WG from encountering the etching solution. (Dr. Gershwin Aff., dated Oct. 17, 2013, ¶ 1, **Ex. 43**.) Such a hypothetical scenario does not undermine Dr. Gershwin's testimony that Walters was actually exposed to etching solution and that exposure caused the onset of WG. (Dr. Gershwin Aff., dated Oct. 17, 2013, ¶ 1, **Ex. 43**.)

6. Experimental Testing is Unethical and Ineffective

Dr. Gershwin testified that it is unethical to perform experimental testing and expose patients to etching solution to evaluate the onset of WG, and the absence of experimentation necessitates the use of analogy to peer-reviewed retrospective studies of naturally occurring incidences of WG arising from exposure to a variety of substances. (*See, e.g.*, Dr. Gershwin Tr. at 21:23 - 22:2, 23:1-13, 23:24 – 24:3, 28:20-23, **Ex. 9**.) The court in *Chapin* recognized the ethical problems with experimental tests involving dangerous substances, such as asbestos. *Chapin*, 274 Mich App at 134. (*See also* discussion of retrospective analysis in scientific literature, *Robelin*, and *Clerc* where prospective testing in impossible or unethical, *supra* § (C)(1).)

Dr. Gershwin further testified that with diseases much more common than WG, it can take decades to find animal models to test the causes of the disease. (*See, e.g.*, Dr. Gershwin Tr. at 35:16 – 36:2, **Ex. 9**.) The difficulties with animal testing of WG are compounded because reproducing the effects of WG in animals requires replication or transfer of *multiple genes* affecting genetic susceptibility. To understand the complexity of replicating multiple genes, consider that multi-billion-dollar funding is necessary to test certain types of cancer that involve the replication or transfer of only a *single gene*. (*See, e.g.*, Dr. Gershwin Tr. at 35:16 – 36:25, **Ex. 9**.) As late as January 2012, scholarly research addressing rodent models for testing ANCA associated vasculitis indicates that "[t]o date there are no good models that replicate the granulomatous lesions found in granulomatosis with polyangiitis (GPA, formerly Wegener's) . . .." Salama, A., and Little, M., *Animal models of ANCA associated vasculitis* (Curr. Opin.

Rheumatol., January 2012), at 1 (**Ex. 44**); *see also* Kallenberg, C., *Pathophysiology of ANCA-Associated Small Vessel Vasculitis* (Curr. Rheumatol Rep, Vol. 12, 2010), at 399 (stating "[u]nfortunately, an animal model for PR3-ANCA—associated Wegener's granulomatosis is not yet available") (**Ex. 45**). Therefore, Dr. Gershwin's reliance upon studies of links between other chemicals and WG is appropriate, particularly where those other chemicals share characteristics with phosphoric acid or actually contain phosphorous. Because testing is inappropriate in this scenario, Dr. Gershwin properly relied upon the SBH methodology and retrospective analysis to evaluate the cause of WG here.

The mechanism of action involving Walters' intense exposure to phosphoric acid followed by the clinical presentation of WG symptoms in the appropriate time period for an immune response is scientifically valuable in this case for the very reason that such a mechanism cannot be ethically reproduced by experimentation. Even if replication were attempted, there is no telling whether the test subjects would have the rare genetic predisposition to WG, which is necessary to perform a successful experiment. (*See, e.g.*, Dr. Gershwin Tr. at 29:25 – 30:4, 30:18 – 31:13, **Ex. 9**.) Consequently, Dr. Gershwin's focus upon studies involving analogous chemicals and the mechanism of action leading to the symptoms of WG follows the SBH methodology and is a scientifically accepted and reliable method for determining causation.

7. Dr. Gershwin's Methods and Reasoning Meet the Factors of MCL 600.2955(1)

As in *Chapin*, the Dr. Gershwin's employment of the methods and reasoning of the SBH methodology and retrospective analysis comport with the factors for reliability set forth in MCL 600.2955 (1). Dr. Gershwin's methods of analyzing analogous chemicals to detect the WG cause and of backtracking from symptom to cause are methods employed in numerous peer-reviewed publications cited above and attached to Defendants' brief before the court below. MCL 600.2955 (1)(b) (opinion and basis subjected to peer review). These same publications

establish that analogous chemicals, silica and pesticides, among others, have been scientifically linked to the onset of WG not by unethical experimental testing but by retrospective studies of the origination of WG observed in WG patients. MCL 600.2955 (1)(a) (opinion and basis subjected to scientific testing). Dr. Gershwin emphasized that the Safety Data Sheet indicates that the phosphoric acid at issue is more chemically potent than the analogous chemicals linked to the onset of WG in the peer-reviewed publications. Consequently, peer-reviewed publications and studies support the link between the onset of WG and analogous chemicals that are *less* potent than the phosphoric acid here.

Dr. Gershwin's analysis of analogous substances and of the mechanism of action are in accord with generally accepted standards governing the application and interpretation of a methodology. MCL 600.2955 (1)(c). Dr. Gershwin's methods are consistent with those in the publications cited where experts worked backward from the WG symptoms to detect an environmental cause. Dr. Gershwin's interpretations are also consistent with those in the publications cited, given that many of the environmental factors linked to WG onset were phosphorous-based substances or solvents with similar chemical characteristics to the phosphoric acid here. In addition, Dr. Gershwin's approach comports with the accepted SBH standards for establishing causation, as discussed previously.

The "error rate" is not a factor that is readily applicable here. MCL 600.2955 (1)(d). Because human testing is unethical and animal testing generally has proven ineffective because of the unreliability of test populations, the publications rely heavily upon retrospective studies of the causes of WG that already manifested in genetically susceptible patients.

The opinion that WG may result from exposure to substances containing phosphate and/or sharing characteristics of phosphate is supported by numerous scholarly publications cited herein and by Defendants in their motion *in limine* below. MCL 600.2955 (1)(e). The publications

consistently link the onset of WG to environmental factors such as silica, hydrocarbons, pesticides, fumes, particulates, and other solvents. Dr. Gershwin's testimony and the pertinent publications establish that many of these chemicals share common characteristics, electrophilic properties, or a key ingredient, phosphorous, with the more potent phosphoric acid here.

The bases for Dr. Gershwin's opinion are reliable in the scientific community, as scientists rely upon the same bases as Dr. Gershwin to reach their conclusions. MCL 600.2955 (1)(f). The published studies and analyses of WG environmental factors use questionnaires and retrospective reviews of environmental factors to determine the cause of WG in patients that have manifested the disease. Here, Dr. Gershwin has identified the acute onset of WG symptoms through medical records following closely in time to the nearly clinical exposure of a person genetically predisposed to WG to a highly potent phosphate substance through direct oral contact with the substance for a period of several hours. The published articles demonstrate that the scientific community would retrospectively trace Walters' condition to potential initiating environmental factors. The published articles further establish that experts would look for environmental factors that cause inflammation of the airways, have electrophilic properties, and involve exposure to potent chemicals, including solvents and substances containing phosphorous. Thus, the basis for Dr. Gershwin's opinion is reliable because it is rooted in a retrospective review from the point of symptoms to an initiating chemical of the appropriate potency, with the appropriate inflammatory effect, involving exposure to the airways, within the appropriate time frame for an immunological response, and which chemical shares characteristics and ingredients of other substances repeatedly linked to the onset of WG.

The methodology employed by Dr. Gershwin is relied upon by experts outside of litigation. MCL 600.2955 (1)(g). The cited publications, and those attached by Defendants to their motion *in limine*, demonstrate that experts regularly analyze the cause of WG by observing symptoms in

a patient and then working backward in time to locate probable environmental factors, such as phosphoric pesticides and farming chemicals as well as solvents, fumes, and other substances bearing properties shared by the phosphoric acid here. Dr. Gershwin has found, *within the appropriate time frame for the immunological response that actually occurred*, a crisis exposure to a potent electrophilic substance containing the same ingredient, phosphorous, as other agents linked to WG onset. Dr. Gershwin's opinions and methodology have the added support of an acute onset of WG symptoms rather than a chronic condition that built over a long period of time in which Walters may have been exposed to other contributing environmental factors. Dr. Gershwin's reliance upon studied effects of analogous substances is consistent with the methods employed in the peer-reviewed publications. Such retrospective methods of study for formulating opinions on WG causation are the scientific standard given the ethical problems with human testing and the genetic complexity of effective animal testing.

D. The Court of Appeals Appropriately Reversed the Circuit Court

The COA again appropriately reversed the Circuit in an opinion dated August 16, 2016. (COA Op. at 11, **Ex. 50**.) The COA extensively analyzed the underlying medical information, the scientific literature submitted, the testimony of Dr. Gershwin, and the standards set forth in MRE 702, MCL 600.2955 (1), and *Chapin*. The COA correctly determined that the Circuit had committed legal error by applying improper rigor to the gatekeeping function and effectively withdrew the fact-finding function from the jury by requiring Plaintiffs to "establish causation and their case prior to trial and to do so definitively." (COA Op. at 11, 12.) The COA further held that the Circuit erred by failing to consider facts supporting Dr. Gershwin's reliability, such as "the nature, duration, intensity, and location of the exposure, the temporal proximity of the immune response to the date of exposure, and the duration and nature of an expected manifestation of WG, *i.e.*, a lengthy battle with sinusitis, which all played a role in Dr.

Gershwin's overall analysis." (COA Op. at 11.)

Defendants attempt to undermine the COA opinion with a variety of ineffectual arguments. Defendants did not raise these arguments and requests below and they are waived or forfeited, as Michigan is generally adheres to a "raise or waive" rule. *Walters v Nadell*, 481 Mich 377, 384 n 14, 387-388; 751 NW2d 431 (2008); *Baxter v Geurink*, 493 Mich 924; 824 NW2d 564 (2013).

Defendants rely upon *Edry v Adelman*, 486 Mich 634, 637, 640-41; 786 NW2d 567 (2010), for the argument that an expert who controverts "authoritative data" that the expert himself recognizes as "authoritative," and proceeds with an opinion without "some basis in fact," may be properly precluded from giving testimony. (Defs' Br. at 10-11.) Defendants, however, provide no "authoritative data" to refute the methods and opinion of Dr. Gershwin. (*See, e.g.*, COA Op. at 12.) Moreover, the relationship between Walters' exposure to phosphoric acid and the perfectly timed maelstrom of WG symptoms is in itself "some basis in fact."

Defendants argue that the Circuit exercised discretion in determining that the connection between pesticides and phosphoric acid was insufficient. (Defs' Br. at 20.) This is incorrect, as the Circuit stated that it found "no articles discussing phosphorus or phosphate exposure" even though it believed that such substances are "fairly common" and are used in "fertilizers," so the Circuit was "a little surprised" there were not any articles. (Hrg. Tr. at 26, **Ex. 11**.) In fact, the articles submitted are replete with discussions of phosphoric pesticides, insecticides, farming chemicals, and agricultural chemicals in addition to discussions of solvents and inhaled substances that are analogous in effect to phosphoric acid in one's mouth. The COA recognized the connection between pesticides and phosphoric acid as well as the comparable characteristics of other substances within the scientific literature, including silica, fumes, particulates, pesticides, and solvents. (COA Op. at 4-5, 9-11.)

Defendants now argue that the gatekeeping analysis should be performed under MCL

600.2955 (2) for a "novel methodology or form of scientific evidence." (Defs' Br. at 8, 22.) However, the articles submitted by Plaintiffs establish that the retrospective analysis employed by Dr. Gershwin has been widely used for decades by scientists producing those peer-reviewed articles. Additionally, the SBH methodology is the "most-adopted methodology for determining causation" and was originally published in 1965. *Chapin*, 274 Mich App at 133.

Defendants argue that the Circuit erroneously ruled without a *Daubert* hearing. (Defs' Br. at 4, 9, 24-25; COA Dissent at 2, 5, **Ex. 49**.) Notably, it was defense counsel who orally argued to the COA that *Plaintiffs* had waived a *Daubert* hearing and should not receive such a hearing. Indeed, while Defendants' original motion *in limine* requested a *Daubert* hearing, defense counsel argued to the Circuit that such a hearing is "not necessary," "I don't believe that we need a hearing," and "I don't think that having the hearing at this point will add anything to the analysis." (Hrg. Tr. at 33-34, **Ex. 11**.) The Circuit asserted that it had no need of a *Daubert* hearing but would allow it, stating "I would be surprised if you were able to prevail at a *Daubert* hearing, but I won't preclude it if you . . . if you want to proceed with a *Daubert* hearing." (Hrg. Tr. at 34, **Ex. 11**.) Plaintiffs submitted relevant testimony of Walters, testimony of Dr. Gershwin, substantial scientific literature, and a motion response brief and a motion for reconsideration brief explicating the scientific support underlying Dr. Gershwin's methodologies and opinions. Indeed, Dr. Gershwin was actively involved in crafting the scientific analysis that has remained constant in Plaintiffs' briefs to the COA and to this Court. (*See* Affs. of Dr. M. Eric Gershwin, **Exs. 17, 43**.) All of Plaintiffs' information was and is before the courts, and if Defendants lost some opportunity to present information by foregoing a *Daubert* hearing, it was by Defendants' own choice. *Nadell*, 481 Mich at 384 n 14, 387-388 (waiver and forfeiture).

Defendants also argue that various courts and the COA dissent hold that the SBH methodology cannot apply absent independent epidemiological data establishing an

"association" between phosphoric acid and WG. (Defs' Br. at 4, 16-17, 18-19-, 23.) To begin with, Defendants' block cite to *Chapin* includes statements by the nationally renowned expert in that case stating that in the SBH methodology, "a strong association between a substance an effect can permit conclusions without statistical epidemiologic data," "no epidemiological studies were needed to show that cyanide gas kills film-recovery plant workers when they are exposed to it," epidemiological evidence "was not needed to draw conclusions on which to base preventive actions," and that "none of the [SBH] factors was dispositive by itself." (Defs' Br. at 18.) *Chapin*, 274 Mich App at 129, 133-34. Defendants argue that in *Chapin*, the parties agreed that mesothelioma is caused by asbestos and no such agreed association exists here. (Defs' Br. at 20-21.) This does not diminish the fact that the *Chapin* expert confirmed that no epidemiologic data is necessary to apply the SBH methodology, nor does it eliminate the analogous epidemiologic data upon which Dr. Gershwin relied in this case. Moreover, to the extent that the parties agreed on one variable in *Chapin*, that asbestos causes mesothelioma, they disagreed upon the sufficiency of exposure. *Chapin*, 274 Mich App at 130-31. In the present case, that second *Chapin* variable, sufficiency of exposure, was satisfied here by Defendants' admission that phosphoric acid can destroy a tooth and should only remain on a tooth for 20 seconds or less, as opposed to Walters sleeping with it all night. (RF Tr. at 26:3-7, 26:11-14, **Ex. 5**; DF Tr. at 45:20-46:10, **Ex. 4**; Resp. 1st Interrogs.-Admit., Admit 8, **Ex. 3**.)

Defendants rely upon *Dunn v Sandoz Pharms Corp*, 275 F Supp 2d 672, 678-79 (MDNC 2003), but that case dealt with an attempt to use the SBH methodology without epidemiological studies, without a reliable scientific methodology, and without any association between two variables. (Defs' Br. at 15-16.) Unlike *Dunn*, Dr. Gershwin's testimony is based upon a decades-old method of retrospective analysis employed by the writers of the WG articles, and Dr. Gershwin relied on numerous epidemiological studies addressing substances with similar

and/or less potent characteristics than phosphoric acid as set forth in detail *supra* and in the COA opinion. Defendants quote *In re Fosamax Prods Liab Litig*, 645 F Supp 2d 164, 188 (SDNY 2009), but immediately following the quote about requiring controlled studies to apply the SBH methodology, the federal court wrote that "[t]he record here is inconclusive on this point," and the court proceeded to deny admissibility because the methodology did not meet the expert's own standards in that case. (Defs' Br. at 16, 23.) Defendants cite *In re Breast Implant Litig*, 11 F Supp 2d 1217, 1234 n 5 (D Colo 1998), but there, the federal court held that Plaintiffs had not addressed the SBH method at all. (Defs' Br. at 16.) None of these cases affect the COA's opinion or Dr. Gershwin's reliability. None of Defendants new arguments merit leave to appeal.

II. *Elher* Is Highly Distinguishable From *Walters*.

Elher does not support the exclusion of Walters' expert. To begin with, *Elher* addressed an expert's opinion on the *standard of care* in a *medical malpractice* case. *Elher* at 2, 7. In *Elher*, there was no dispute over how the plaintiff's common bile duct was injured – it was inadvertently clipped during gallbladder removal surgery. *Id*. at 3. The issue there was whether clipping a bile duct was a breach of the *standard* of care supporting medical malpractice. *Walters* is an ordinary negligence case that does not require an opinion on the standard of care. (*See* Order Granting Pls.' Mot. for Partial Summary Disp., dated June 27, 2013, **Ex. 13**.) An ordinary layperson knows that a dentist should not give a patient *phosphoric acid* for the patient to use in her *teeth whitening dental trays* and the Defendants here have admitted such acid should never be provided to a patient. (*See* **Ex. 3**, Defs.' Resp. to Pls.' First Interrogs. And Reqs. to Admit., "Resp. 1st Interrogs.-Admit.," Interrog. 18.)

Unsupported expert opinion on the "standard" of care in *Elher* is different from the admittedly improper act of dispensing phosphoric acid in *Walters*. The *Elher* expert's opinion on the "standard" of care necessarily required an analysis of what the "standard" was for the

medical community. Dr. Gershwin did not need to testify about the "standard" of care for avoiding the onset of WG. Instead, the question here is whether Dr. Gershwin's testimony is based upon reliable principles and methods for determining causation of and damages from WG. Thus, the *Elher* expert was *defining* a "standard" in the medical community while Dr. Gershwin was *following* methods employed throughout the scientific community and illustrated in scientific literature to trace WG from effect back to its cause. The *Elher* expert asserted only his own unsupported "belief" about a medical "standard" while Dr. Gershwin has put into practice the same methods of analysis, such as retrospective analysis, that are evident in the scientific literature submitted by Plaintiffs spanning decades of scientific efforts to trace the cause of WG.

The decision in *Elher* was based upon the expert's reliance on his own "belief system" or "his own beliefs" without "any supporting authority," with "no medical literature supporting his opinion," and without "any other support for [the expert's] opinion." *Elher* at 8, 15. This Court precluded the expert opinion based upon "the lack of supporting literature, combined with the lack of any other form of support." *Id*. at 16, also at 3 ("did not provide any supporting authority for his opinion"). The Walters' expert has provided voluminous documents, peer-reviewed literature, and his own affidavits, supporting the potency of the phosphoric acid chemical, the pathogenesis of the disease, the rarity of WG genetic predisposition, the chemical data information and dangers when exposed to water, the duration and intensity of exposure, the key role of respiratory inflammation in WG onset combined with the oral exposure here, the studied impact of similar chemicals in the onset of WG, including phosphorous based chemicals like pesticides, the physical changes in Walters shown in medical records, the textbook immunological response time from exposure to onset of symptoms, the manifestation of WG-related symptoms such as sinusitis, the scientific community's common reliance upon retrospective analysis in tracing effect to cause for WG and other untestable vasculitis, and the

application of the SBH methodology for evaluating cause where experimental testing is not possible. (*See, e.g.*, **Exs. 6-8, 15, 17-45**.) The COA evaluated the phosphoric acid safety data sheet, Walters' medical records, and 28 peer-reviewed scientific articles, and the COA filled *eight pages* citing factual information supporting the reliability of Dr. Gershwin's scientific analysis. (COA Opinion, **Ex. 50**.) *Walters* is not a case, such as *Elher*, where the plaintiff's expert could point to *nothing* in support of his testimony aside from his own belief.

Moreover, Defendants in *Walters* have not provided the type of evidence submitted by the defendants in *Elher*. In *Elher*, the defendants provided peer-reviewed literature indicating that inadvertently cutting the bile duct during gallbladder removal surgery does not constitute negligence but occurs as a result of misperception errors arising from the lack of depth perception when using a two-dimensional video to perform surgery. *Elher* at 5, 13-14. One of the concluding remarks in the *Elher* opinion was the Court's focus on the presence of contradictory medical literature. *Id*. at 16. Defendants in *Walters* have provided no peer-reviewed literature suggesting that Dr. Gershwin's reasoning and methodology is scientifically unreliable or that extended oral exposure to a highly caustic chemical, such as phosphoric acid, is insufficient to cause the onset of WG.

Another distinction in *Elher* is that it did not even address the SBH methodology or retrospective analysis that are important to Dr. Gershwin's opinion and the scientific community's study of causes of WG. Indeed, *Elher* did not address any methods for assessing cause and effect of an injury because the cause of injury in *Elher* was undisputed. *Elher*, at 3.

Elher confirmed that not all of the MCL 600.2955 factors are relevant in every case and, specifically, that scientific testing and replication factor did not fit the medical opinion at issue. *Elher*, at 14-15. The Court in *Elher* held that the trial court *abused its discretion* in relying upon the scientific testing factor. *Elher*, at 15. Likewise, it would be an abuse of discretion for this

Court to focus on whether experimental testing has been performed by exposing potential WG patients to phosphoric acid. Defendants have pressed the courts to compel Plaintiffs to produce a study showing WG patients that were exposed to phosphoric acid. The COA properly rejected a requirement of such testing, stating that "we are not prepared to preclude Dr. Gershwin's testimony simply because there is not a specific study showing that exposure to phosphoric acid causes WG." (COA Opinion at 12.) As in *Elher*, the COA here properly determined that testing is not a relevant factor in this case, where testing might severely injure or kill the human subject.

In summary, *Elher* found that (1) the plaintiffs failed to provide support for their experts' opinion, (2) scientific literature contradicted the expert's opinion, and (3) this Court agreed that scientific testing is not relevant in every case. In *Walters*, (1) the COA has recognized substantial scientific literature, medical records, and chemical data supporting Dr. Gershwin's methods and analysis, (2) Defendants have provided no scientific information refuting Dr. Gershwin's methods and analysis, and (3) the COA properly determined that scientific testing is not relevant in this case. As discussed more fully in the Procedural Background, *supra*, the COA held that "Dr. Gershwin's opinion was supported by myriad variables or factors," as opposed to the *Elher* expert's reliance purely upon his personal beliefs. (COA Op. at 15.)

CONCLUSION

For the reasons set forth above, Plaintiffs respectfully request that this Honorable Court deny Defendants' Application for Leave to Appeal (after Remand) or affirm the COA opinion.

Respectfully submitted,

HERTZ SCHRAM PC

Dated: October 25, 2016

By: /s/ Daniel W. Rucker
Daniel W. Rucker (P67832)
Attorney for Plaintiffs/Appellees

INDEX OF EXHIBITS

Exhibit 20: Lane, S., Watts, R., and Scott, D., *Epidemiology of Systemic Vasculitis* (Curr. Rheumatology Reports, Vo. 7, 2005)

Exhibit 21: Lee, Y.H., *et al*., *The protein tyrosine phosphatase nonreceptor 22 C1858T polymorphism and vasculitis: a meta-analysis* (Mol Biol Rep, ed. 39, 2012)

Exhibit 22: Safety Data Sheet

Exhibit 23: Chen, M. and Kallengberg, C., *The environment, geoepidemiology and ANCA-associated vasculitides* (Autoimmunity Reviews ed. 9, 2010)

Exhibit 24: Sibelius, U., *et al*., *Wegener's Granulomatosis: Anti-proteinase 3 Antibodies Are Potent Inductors of Human Endothelial Cell Signaling and Leakage Response* (J. Exp. Med., Vol. 187, No. 4, Feb. 16, 1998)

Exhibit 25: Lane, S., Watts, R., *et. al*, *Are Environmental Factors Important in Primary Systemic Vasculitis?* (Arthritis & Rheumatism, Vol. 48. No. 3, 2003)

Exhibit 26: Duna, G.F., Cotch, M.F., *et. al*, *Wegener's granulomatosis: Role of environmental exposures* (Clinical and Experimental Rheumatology, Vol. 16, 1998)

Exhibit 27: Betteridge, D., Thompson, M., Baker, A.D., and Kemp, N.R., *Photoelectron Spectra of Phosphorus Halides, Alkyl Phosphites and Phosphates, Organo-Phosphorus Pesticides, and Related Compounds* (Analytical Chemistry, Vol. 44 No. 12, 1972)

Exhibit 28: GoodGuide, *Organophosphate Pesticides: Dialkyl Phosphate Metabolites* (Scorecard 2011)

Exhibit 29: National Biomonitoring Program, *Organophosphorus Insecticides: Dialkyl Phosphate Metabolites* (United States Centers for Disease Control and Prevention, 2013)

Exhibit 30: Gershwin, M.E., *et al*., *Electrophile-modified lipoic derivatives of PDC-E2 elicits anti-mitochondrial antibody reactivity* (Journal of Autoimmunity ed. 37, 2011)

Exhibit 31: Husain, K., *Delayed Neurotoxicity of Organophosphorus Compounds* (J. of Environ. Immun. and Toxicology, Vol. 1, issue 1, Mar./Apr. 2013)

Exhibit 32: Metcalf, R.I., *et al*., *Meta-sulfurpentafluorophenyl Diethyl Phosphate and Meta-sulfurpentafluorophenyl N-methylcarbamate as Insecticides and Anticholinesterases* (J. Of Economic Entomology, Vol. 55, No. 3, June 1962)

Exhibit 33: Yamashita, T., *et al.*, *Simultaneous removal of colour, phosphorus and disinfection from treated wastewater using an agent synthesized from amorphous silica and hydrated lime* (Environ Technol., ed. 34, 2013)

Exhibit 34: Smith, K., *et al*., *New Reagent Systems for Electrophilic Chlorination of Aromatic Compounds: Organic Chlorine-Containing Compounds in the Presence of Silica* (Dept. of Chemistry, Univ. College of Swansea, U.K., Dec. 1985)

Exhibit 35: Occupational Safety and Health Association, *Occupational Exposure to Respirable Crystalline Silica – Review of Health Effects Literature and Preliminary Quantitative Risk Assessment* (Docket OSHA-2010-0034)

Exhibit 36: *Organophosphorus Insecticides: Dialkyl Phosphate Metabolites* (United States Centers for Disease Control and Prevention, 2009)

Exhibit 37: Petty, C.S., *et al.*, *Organic Phosphate Insecticides – A Survey of Blood Cholinesterase Activity of Exposed Agricultural Workers in Louisiana, 1957* (Am. J. Public Health, Vol. 49, No. 1, Jan. 1957)

Exhibit 38: Blanc-Lapierre, A., *et al*., *Cognitive Disorders and Occupational Exposure to Organophosphates: Results From the PHYTONER Study* (Am. J. of Epidemiology, Vol. 177, No. 10, 2013)

Exhibit 39: Wang, H.P., *et al*., *H NMR-based metabonomic analysis of the serum and urine of rats following subchronic exposure to dichlorvos, deltamethrin, or a combination of these two pesticides* (Chemico-Biological Interactions, Vol. 203, 2013)

Exhibit 40: Marx, R., *Uncovering the Cause of "Phossy Jaw" Circa 1858 to 1906: Oral and Maxillofacial Surgery Closed Case Files—Case Closed* (Am. Assoc. of Oral and Maxillofacial Surgeons, 2008)

Exhibit 41: Sanfilippo, F., *et al*., *Crystalline Deposits of Calcium and Phosphorus* (Arch. Pathol. Lab. Med., Vol. 105, Nov. 1981)

Exhibit 42: Thedrez, A., *et al*., *IL-21-Mediated Potentiation of Antitumor Cytolytic and Proinflammatory Responses of Human Vγ9Vδ2 T Cells for Adoptive Immunotherapy* (The J. of Immunology, 2009)

Exhibit 43: Aff. of Dr. M. Eric Gershwin, dated Oct. 17, 2013

Exhibit 44: Salama, A., and Little, M., *Animal models of ANCA associated vasculitis* (Curr. Opin. Rheumatol., January 2012)

Exhibit 45: Kallenberg, C., *Pathophysiology of ANCA-Associated Small Vessel Vasculitis* (Curr. Rheumatol Rep, Vol. 12, 2010)

Exhibit 46: *Robelin v Spectrum Health Hosps*, unpub'd op *per curiam* of the Court of Appeals, issued Sept 10, 2009 (Dkt. No. 279780); 2009 Mich App LEXIS 1865

Exhibit 47: *Clerc v Chippewa County War Mem Hosp*, unpub'd op *per curiam* of the Court of Appeals, issued Nov 14, 2013 (Dkt. No. 307915); 2013 Mich App LEXIS 1823

Exhibit 48: January 29, 2015 COA Order Reversing Exclusion of Dr. Gershwin

Exhibit 49: January 29, 2015 COA Dissent Regarding Order Reversing Exclusion of Dr. Gershwin

Exhibit 50: August 16, 2016 COA Order Reversing Exclusion of Dr. Gershwin, On Remand

Exhibit 51: *Elher v Misra*, 499 Mich 11; 878 NW 2d 790 (Dkt. No. 150824, 2016)

Exhibit 52: April 25, 2016, MSC Order Vacating and Remanding re *Elher*

PROOF OF SERVICE

I hereby certify that on ***October 25, 2016***, I electronically filed ***Plaintiffs/Appellees' Response to Defendants/Appellants' Application for Leave to Appeal (After Remand)*** with the Clerk of the Court using the TrueFiling file and serve system which will send notification of such filing to counsel of record.

/s/ Shannon Shaw